Cochrane Library

Cochrane Database of Systematic Reviews

Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews (Review)

Keus F, Gooszen HG, van Laarhoven CJHM

Keus F, Gooszen HG, van Laarhoven CJHM.
Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews.
Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD008318.
DOI: 10.1002/14651858.CD008318.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Overview of Reviews]

Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews

Frederik Keus[1], Hein G Gooszen[2], Cornelis JHM van Laarhoven[3]

[1]Surgery, University Medical Center St Radboud, Nijmegen, Netherlands. [2]Department of Surgery, University Medical Center Utrecht, Utrecht, Netherlands. [3]Department of Surgery 690, University Medical Center St. Radboud, GA Nijmegen, Netherlands

Contact address: Frederik Keus, Surgery, University Medical Center St Radboud, Geert Grooteplein-Zuid 16, Nijmegen, Gelderland, 6525 GA, Netherlands. erickeus@hotmail.com.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2010.

Citation: Keus F, Gooszen HG, van Laarhoven CJHM. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD008318. DOI: 10.1002/14651858.CD008318.

ABSTRACT

Background

Patients with symptomatic cholecystolithiasis are treated by three different techniques of cholecystectomy: open, small-incision, or laparoscopic. There is no overview on Cochrane systematic reviews on these three interventions.

Objectives

To summarise Cochrane reviews that assess the effects of different techniques of cholecystectomy for patients with symptomatic cholecystolithiasis.

Methods

The *Cochrane Database of Systematic Reviews* (CDSR) was searched for all systematic reviews evaluating any interventions for the treatment of symptomatic cholecystolithiasis (Issue 4, 2009).

Main results

Three systematic reviews that included a total of 56 randomised trials with 5246 patients are included in this overview of reviews. All three reviews used identical inclusion criteria for trials and participants, and identical methodological assessments.

Laparoscopic versus small-incision cholecystectomy
Thirteen trials with 2337 patients randomised studied this comparison. Bias risk was relatively low. There was no significant difference regarding mortality or complications. Total complications of laparoscopic and small-incision cholecystectomy were high, ie, 17.0% and 17.5%. Total complications (risk difference, random-effects model -0.01 (95% confidence interval (CI) -0.07 to 0.05)), hospital stay (mean difference (MD), random-effects -0.72 days (95% CI -1.48 to 0.04)), and convalescence were not significantly different. Trials with low risk of bias showed a quicker operative time for small-incision cholecystectomy (MD, low risk of bias considering 'blinding', random-effects model 16.4 minutes (95% CI 8.9 to 23.8)) while trials with high risk of bias showed no statistically significant difference.

Laparoscopic versus open cholecystectomy
Thirty-eight trials with 2338 patients randomised studied this comparison. Bias risk was high. Laparoscopic cholecystectomy patients had a shorter hospital stay (MD, random-effects model -3 days (95% CI -3.9 to -2.3)) and convalescence (MD, random-effects model -22.5

days (95% CI -36.9 to -8.1)) compared with open cholecystectomy but did not differ significantly regarding mortality, complications, and operative time.

Small-incision versus open cholecystectomy
Seven trials with 571 patients randomised studied this comparison. Bias risk was high. Small-incision cholecystectomy had a shorter hospital stay (MD, random-effects model -2.8 days (95% CI -4.9 to -0.6)) compared with open cholecystectomy but did not differ significantly regarding complications and operative time.

Authors' conclusions

No statistically significant differences in the outcome measures of mortality and complications have been found among open, small-incision, and laparoscopic cholecystectomy. There were no data on symptom relief. Complications in elective cholecystectomy are high. The quicker recovery of both laparoscopic and small-incision cholecystectomy patients compared with patients on open cholecystectomy justifies the existing preferences for both minimal invasive techniques over open cholecystectomy. Laparoscopic and small-incision cholecystectomies seem to be comparable, but the latter has a significantly shorter operative time, and seems to be less costly.

PLAIN LANGUAGE SUMMARY

Open, small-incision, and laparoscopic cholecystectomy seem comparable with regard to mortality and complications

Gallstones are one of the major causes of morbidity in western society. Prevalence of persons with asymptomatic and symptomatic gallstones varies between 5% and 22%. There is consensus that only patients with symptomatic gallstones need treatment. Three different operation techniques for removal of the gallbladder exist: the classical open operation technique and two minimally invasive procedures, the laparoscopic and the small-incision technique. This overview evaluates the three surgical procedures and comprises fifty-six trials with 5246 patients randomised.

Complication proportions in all three techniques are high, but there seem to be no significant differences in mortality and complications between the three operation techniques. Both minimally invasive techniques have advantages over the open operation considering postoperative recovery. This overview of three Cochrane Hepato-Biliary Group systematic reviews shows that the laparoscopic and the small-incision operation should be considered equal regarding patient-relevant outcomes (mortality, complications, hospital stay, and convalescence). Operative time seems to be quicker and costs seem to be lower using the small-incision technique.

The question today is why the laparoscopic cholecystectomy has become the standard treatment of cholecystectomy for patients with symptomatic cholecystolithiasis without the evidence being present. We were unable to find any arguments supporting the 'gold standard' status of laparoscopic cholecystectomy.

In future trials, research should concentrate more on outcomes that are relevant to patients (eg, complications and symptom relief). Furthermore, the execution of the trials should comply with CONSORT requirements (www.consort-statement.org).

BACKGROUND

Gallstones are one of the major causes of morbidity in western society. In many persons gallstones remain asymptomatic. Treatment is required only in persons with symptomatic gallstones (NIH Consensus conference 1993). Prevalence of persons with asymptomatic and symptomatic gallstones varies between 5% and 22% in the USA, and the total estimated number of people with gallstones is 20 million (based on 290 million inhabitants) (Legorreta 1993; Everhart 1999). Prevalence of persons with asymptomatic and symptomatic gallstones in Europe shows similar distributions varying between 25 and 50 million persons (based on 500 million inhabitants in 32 countries) (Jensen 1991; Attili 1995). It is estimated that the yearly incidence of symptomatic cholecystolithiasis is up to 2.2 per thousand inhabitants (Steiner 1994).

Description of the condition

There is general agreement supported by limited evidence that gallstone carriers with vague symptoms should not undergo cholecystectomy, whereas gallstone carriers with one or more biliary colic should be offered operation (Scott 1992; NIH Consensus conference 1993; Neugebauer 1995). A biliary colic is typically defined by severe pain in the epigastrium or the right hypochondrium, eventually radiating to the back, persisting for one to five hours, often waking the patient during the night, and sometimes provoked by meals. Classically, patients experience the need to move around, and there is no typical sign at physical examination. The presence of gallstones is usually confirmed by ultrasound examination (Johnston 1993).

Description of the interventions

Cholecystectomy is the preferred treatment in symptomatic cholecystolithiasis and is one of the most frequently performed operations. The annual number of cholecystectomies in the USA exceeds 500,000 patients (Olsen 1991; NIH Consensus conference 1993; Roslyn 1993). Until the late 1980s, the classical open cholecystectomy was the gold standard for treatment of symptomatic cholecystolithiasis (Traverso 1976). In the early 1970s, small-incision cholecystectomy was introduced as a minimal invasive procedure (Dubois 1982; Goco 1983). As incisions for cholecystectomy were shortened, morbidity and complications seemed to decline (Dubois 1982; Goco 1983) and patients recovered faster. Laparoscopic cholecystectomy was first performed in 1985 (Mühe 1986) and rapidly became the method of choice for surgical removal of the gallbladder (NIH Consensus conference 1993), although the evidence of superiority over small-incision cholecystectomy was absent. This rising popularity was based on assumed lower morbidity and complication proportions, and a quicker postoperative recovery compared to open cholecystectomy. Laparoscopic cholecystectomy seemed superior to open cholecystectomy (Deziel 1993; Downs 1996; Shea 1996) and to small-incision cholecystectomy (Ledet 1990; O'Dwyer 1990; Olsen 1993; Tyagi 1994; Seale 1999). However, the mentioned studies are non-randomised trials, and accordingly they may not provide a fair assessment of the effects of the interventions.

How the intervention might work

Removal of the gallbladder including its content prevents recurrence of colics caused by gallbladder stones. However, patients often do not present with the classical symptoms of biliary colics. Therefore, patients with non-classical symptoms or asymptomatic gallstones may be offered gallbladder removal in the presence of symptoms originating from other abdominal organs. In fact, abdominal complaints wrongly attributed to co-existent gallstones could explain the relatively high proportions of failures in symptom relief by cholecystectomy.

Why it is important to do this overview

Laparoscopic cholecystectomy is the treatment of choice by consensus in patients with symptomatic cholecystolithiasis (NIH Consensus conference 1993), while high level evidence for this consensus is lacking. Recently, three Cochrane Hepato-Biliary Group systematic reviews have been conducted comparing different surgical techniques for gallbladder removal in these patients (Keus 2006a; Keus 2006b; Keus 2006c). An overview of the reviews considering the surgical treatment of symptomatic cholecystolithiasis is lacking. This was the reason for preparing this overview of systematic reviews.

OBJECTIVES

The objective was to evaluate the beneficial and harmful effects of different types of cholecystectomy for patients with symptomatic cholecystolithiasis. We wanted to assess whether laparoscopic, small-incision, or open cholecystectomy are different in terms of primary outcomes (mortality, complications, and relief of symptoms) or secondary outcomes (conversions to open cholecystectomy, operative time, hospital stay, and convalescence). When data were available, differences in other secondary outcomes like analgesic use, postoperative pain, pulmonary function, and costs were also compared.

METHODS

The overview was conducted according to the recommendations by *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and the *Cochrane Hepato-Biliary Group Module* (Gluud 2009).

Criteria for considering reviews for inclusion

Only Cochrane reviews were considered for inclusion in this overview. Non-Cochrane reviews were not planned to be included in this overview.

Participants

Participants in the included reviews were patients suffering from symptomatic cholecystolithiasis. Reviews on participants with acute cholecystitis were excluded from this overview for reasons of heterogeneity in patient populations.

Interventions

Only surgical treatments for symptomatic cholecystolithiasis were considered. Three different techniques for cholecystectomy were recognised: open, small-incision, and laparoscopic cholecystectomy. The following classifications of the surgical procedures (based on intention-to-treat) were used:

Laparoscopic cholecystectomy includes those procedures that are started as a laparoscopic procedure; ie, any kind of laparoscopic cholecystectomy with creation of a pneumoperitoneum (by Veress needle or open introduction) or mechanical abdominal wall lift, irrespective of the number of trocars used.

Only if 'small-incision', 'minimal access', 'minilaparotomy', or similar terms as intended terms were mentioned in the primary classification of the procedure, then the surgical intervention was classified as a 'small-incision' cholecystectomy (ie, length of incision less than 8 cm). The incision length of up to 8 cm was chosen arbitrarily as most authors had used this length as a cut-off point between small-incision and (conversion to) open cholecystectomy.

All other surgical interventions for gallbladder removal were classified as 'open cholecystectomy'; this traditional procedure can be carried out through a larger, ie, ≥ 8 cm, subcostal incision or median laparotomy.

Outcomes of interest

Both primary and secondary outcome measures were considered. Primary outcome measures were mortality, complications (including subcategories), and symptom relief. Secondary outcome measures were all other, less important, outcome measures evaluated, if any. All outcomes reported in the three systematic reviews were included.

Search methods for identification of reviews

As only Cochrane reviews were considered for inclusion in this overview of reviews, *The Cochrane Database of Systematic Reviews* (CDSR), Issue 4, 2009, was searched (Table 1). The systematic reviews had to evaluate any surgical interventions for the treatment of symptomatic cholecystolithiasis. The term 'cholecystectomy' was entered and restricted to title, abstract, or keywords. As describing an operation of the gallbladder in medical terms without the word cholecystectomy is impossible, a maximal sensitive search with the term cholecystectomy was achieved. No other databases were searched. No restrictions in the inclusion criteria of the identified reviews were applied regarding participants, details of the interventions, or outcomes of interest.

Data collection and analysis

The following methods on data collection and data analyses were used in the overview of reviews.

Selection of reviews

The selection process of Cochrane reviews was performed based on the criteria for considering reviews for inclusion. Cochrane reviews were included when comparisons were made between any kind of surgery in patients suffering from symptomatic cholecystolithiasis.

Data extraction and management

Data from the Cochrane reviews were extracted independently by two authors and regarding outcomes not reported in the reviews by one author (FK). Disagreements were resolved by consensus. In case of missing data, all original reports of included trials were assessed and additional analyses of missing data were performed if appropriate.

Assessment of methodological quality of included reviews

Quality of included reviews

The quality of the included reviews was taken into account. We described the quality of the reviews in a narrative way. The risk of systematic errors (bias) in systematic reviews is influenced by the risks of systematic errors (bias) in the primary trials included in the systematic review.

Quality of evidence in included reviews

Only recently, methodological quality assessment is recommended according to the GRADE recommendations (Atkins 2004; Atkins 2005; Guyatt 2008; Guyatt 2008a). However, the quality of evidence of the included trials in the reviews, prior to this new assessment tool, was assessed according to four components assessing risk of bias: generation of the allocation sequence, allocation concealment, blinding, and follow-up. We described the bias risk of the included trials as they were assessed in the included reviews.

Data synthesis

Data were extracted from the underlying systematic reviews, and the summary findings were presented in tables (Table 2; Table 3; Table 4; Table 5; Table 6; Table 7). Data were extracted from direct comparisons, and no indirect comparisons were made since evidence from indirect comparisons may be less reliable than evidence from direct (head-to-head) comparisons. All data rest on intention-to-treat analyses.

RESULTS

A total of 14 systematic reviews were identified by the search strategy in the Cochrane Database of Systematic Reviews. Three of these systematic reviews could be included (Keus 2006a; Keus 2006b; Keus 2006c) (Table 2). For detailed descriptions of all results, we refer to the three individual Cochrane Hepato-Biliary Group reviews (Keus 2006a; Keus 2006b; Keus 2006c) and a paper publication in which all the three reviews were updated (Keus 2008a).

Description of included reviews

The included three reviews contain a total of 56 randomised trials with 5246 patients randomised. One of the randomised trials (Coelho 1993) was included in all the three systematic reviews because it had three parallel-group comparisons (Keus 2006a; Keus 2006b; Keus 2006c).

The *Cochrane Database of Systematic Reviews* in *The Cochrane Library* (Issue 4, 2009) was searched to identify reviews for this overview of reviews. The three systematic reviews used identical inclusion criteria for inclusion of trials. Only randomised trials were included. Identical criteria for types of participants were used. Three reviews were included which compared open, small-incision, and laparoscopic cholecystectomy (Table 2).

Identical outcome measures were considered in the three systematic reviews (Keus 2006a; Keus 2006b; Keus 2006c). Primary outcomes were distinguished from secondary outcome measures (Table 3; Table 4). Primary outcomes were mortality and complications. Complications were subcategorised into four subcategories (intra-operative, bile duct injuries, minor complications, and severe complications) apart from total complication proportions. Secondary outcomes were convalescence (including return to normal activity and return to work), operative time, and hospital stay. No data were available considering symptom relief.

Methodological quality of included reviews

The methodological quality of the randomised clinical trials in the included reviews was evaluated by assessing the following risk of bias components: generation of the allocation sequence, allocation concealment, blinding, and follow-up (Higgins 2006; Gluud 2009). Each component was assessed adequate, unknown ('not performed' for blinding), or inadequate. Subgroup analyses were performed based on these assessments. The risk of bias of the included trials was considered high both in the small-incision versus open cholecystectomy and in the laparoscopic versus open cholecystectomy comparisons, while it was considered relatively low in the laparoscopic versus small-incision cholecystectomy comparison.

Effect of interventions

Outcomes reported in the systematic reviews

Summary of findings were reported in Table 5, Table 6, and Table 7.

Mortality

Mortality was not reported in all seven trials in the small-incision versus open cholecystectomy comparison. Mortality was reported in 14 trials in the laparoscopic versus open cholecystectomy comparison and in seven trials in the laparoscopic versus small-incision cholecystectomy comparison.

We found no significant differences in mortality between the three techniques. Mortality rates were low (up to 0.09%) in the different comparisons.

Complications

Complications were categorised into intra-operative, minor, severe, bile duct injury complications, and total complication proportions. There were no significant differences in any of the complication categories.

Intra-operative complications

There were zero intra-operative complications in the small-incision versus open cholecystectomy comparison. In the laparoscopic versus open cholecystectomy comparison, the intra-operative complication proportions were 0.9% and 0.1%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the intra-operative complications were 13.1% and 7.6%, respectively.

We found no significant differences in the intra-operative complications between the three techniques.

Minor complications

In the small-incision versus open cholecystectomy comparison, the minor complication proportions were 8.6% and 6.8%, respectively. In the laparoscopic versus open cholecystectomy comparison, the minor complication proportions were 2.1% and 3.1%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the minor complications were 8.3% and 9.2%, respectively.

We found no significant differences in the minor complications between the three techniques.

Severe complications

In the small-incision versus open cholecystectomy comparison, the severe complication proportions were 1.4% and 2.5%, respectively. In the laparoscopic versus open cholecystectomy comparison, severe complication proportions were 2.2% and 6.8%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the severe complications were 4.0% and 4.2%, respectively.

We found no significant differences in the severe complications between the three techniques.

Bile duct injury

In the small-incision versus open cholecystectomy comparison, zero bile duct injuries were reported. In the laparoscopic versus open cholecystectomy comparison, the proportion of bile duct injuries was 0.2% in both groups. In the laparoscopic versus small-incision cholecystectomy comparison, the bile duct injury proportions were 1.2% and 1.9%, respectively (risk difference, fixed-effect model -0.01, 95% CI -0.02 to 0.00). The difference is mainly caused by eight patients with bile leakage with unknown origin and conservative treatment in the small-incision group (five patients from one trial).

We found no significant differences in the bile duct injuries between the three techniques.

Total complications

In the small-incision versus open cholecystectomy comparison, no significant differences were found; the total complication proportions were 9.9% and 9.3%, respectively (risk difference 0.00, 95% CI -0.06 to 0.07).

In the laparoscopic versus open cholecystectomy comparison, the total complication proportions were 5.4% and 10.1%, respectively. Although significant differences were found including all trials and in the trials with high risk of bias (risk difference -0.04, 95% CI -0.07 to -0.01), no significant difference was found in the trials with low risk of bias (risk difference -0.01, 95% CI -0.05 to 0.02).

No significant differences were observed in the total complication proportions in the laparoscopic versus small-incision cholecystectomy comparison (26.6% and 22.9%, respectively) (risk difference -0.01, 95% CI -0.07 to 0.05) with 1.6% re-operation in both groups. We also summarised the complications in trials, in which three or more bias components were considered adequate. There was no significant difference in the proportions of total complications between laparoscopic and small-incision cholecystectomy when only trials with low risk of bias were included. However, in the trials with low risk of bias the complication proportions in both groups were higher than the complication proportions in the trials with high risk of bias.

We found no significant differences in the total complications between the three techniques.

Conversions

Conversion proportions in the small-incision versus open cholecystectomy comparison and in the laparoscopic versus open cholecystectomy comparison have not been reported. No significant differences in conversion proportions were found in the laparoscopic versus small-incision cholecystectomy comparison (13.4% and 16.1%, respectively; risk difference 0.00, 95% CI -0.05 to 0.04).

Operative time

We did not observe significant differences considering operative time in the small-incision versus open cholecystectomy comparison (MD 1.94 minutes, 95% CI -1.37 to 5.25).

We found no significant differences considering operative time in the laparoscopic versus open cholecystectomy comparison (MD 3.79 minutes, 95% CI -4.88 to 12.46).

There is a significant difference in operative time in the laparoscopic versus small-incision cholecystectomy comparison. Small-incision cholecystectomy is significantly faster to perform (MD 9.20 minutes, 95% CI 2.06 to 16.35). Trials with low risk of bias showed significant differences (MD, trials with low risk of bias considering 'blinding', random-effects model 16.4 minutes (95% CI 8.9 to 23.8)), while trials with high risk of bias showed no significant difference.

Hospital stay

In the small-incision versus open cholecystectomy comparison, hospital stay was significantly shorter using the small-incision technique (MD -2.78 days, 95% CI -4.94 to -0.62).

In the laparoscopic versus open cholecystectomy comparison, hospital stay was significantly shorter using the laparoscopic operation (MD -3.07 days, 95% CI -3.89 to -2.26).

In the laparoscopic versus small-incision cholecystectomy comparison, no significant difference regarding hospital stay was present in the trials with low risk of bias (MD, trials with low risk of bias considering 'blinding', random-effects model -0.56 days (95% CI -1.24 to 0.11)), but a significant difference was present in the trials with high risk of bias (MD, trials with high risk of bias considering 'blinding', random-effects model -1.08 days (95% CI -1.88 to -0.28)).

Convalescence

As convalescence can also be measured according to return to work and return to normal activity (at home), different analyses were conducted.

In the small-incision versus open cholecystectomy comparison, no data were available considering work leave. In the laparoscopic versus open cholecystectomy comparison, a significant difference was found with the laparoscopic cholecystectomy showing a shorter work leave (MD -22.51 days, 95% CI -36.89 to -8.13). In the laparoscopic versus small-incision cholecystectomy comparison, no significant difference between the techniques regarding work leave was found (MD, random-effects model -0.43 days (95% CI -4.37 to 3.51)).

No results were reported in the small-incision versus open cholecystectomy comparison and in the laparoscopic versus open cholecystectomy comparison. Data on convalescence to normal activity were available in the laparoscopic versus small-incision cholecystectomy comparison only: no significant difference was found considering convalescence to normal activity (at home) (MD, trials with low risk of bias considering 'blinding', random-effects model 0.79 days (95% CI -5.96 to 7.55)).

DISCUSSION

Summary of main results

The present overview of three Cochrane Hepato-Biliary Group systematic reviews contains at least nine major findings. First, the comparison of the clinical outcome of open, small-incision, or laparoscopic cholecystectomy has been well tested in 56 randomised clinical trials, and the risk of bias has been relatively low in laparoscopic versus small-incision cholecystectomy trials, but generally high in laparoscopic versus open cholecystectomy trials and in the small-incision versus open cholecystectomy trials. Trials with inadequate methodological components carry a higher risk of bias (Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008). Second, laparoscopic cholecystectomy does not seem to carry more bile duct injuries than small-incision or open cholecystectomy. In this comparison one has to assume that especially interested and skilled surgeons conducted the trials and carried out the interventions. Therefore, everyday clinical practice and complication rates ought to be followed through clinical databases and compared to benchmark values (Winkel 2007). Third, the total numbers of patients with complications are high and not significantly different for the three procedures. Fourth, small-incision cholecystectomy takes significantly less time to perform than laparoscopic cholecystectomy. Fifth, both of the minimally invasive techniques have a shorter hospital stay compared with open cholecystectomy. Hospital stay after laparoscopic and small-incision cholecystectomy was not significantly different. Sixth, convalescence after laparoscopic and small-incision cholecystectomy measured by return to work and return to normal activity was not significantly different. Laparoscopic cholecystectomy shows a shorter convalescence compared with open cholecystectomy. Seventh, there seem to be no significant differences in pulmonary function and analgesic use for laparoscopic and small-incision cholecystectomy (see below). Eighth, there seem to be no significant differences in health status among laparoscopic and small-incision cholecystectomy (see below). Ninth, costs appear to be lower from different perspectives when using the small-incision technique (see below).

Overall, both laparoscopic and small-incision cholecystectomy show quicker convalescence compared with open cholecystectomy. Small-incision cholecystectomy is quicker to perform and associated with lower costs from different perspectives compared with laparoscopic cholecystectomy.

Overall completeness and applicability of evidence

After having conducted the three Cochrane Hepato-Biliary Group reviews, it appeared that both of the minimal-invasive techniques were advantageous compared with the open cholecystectomy. Both minimal-invasive techniques seemed to be comparable. Therefore, we questioned the reliability of our findings of the laparoscopic versus small-incision cholecystectomy review with respect to the primary outcome measures. We performed two additional studies; one assessing the robustness of findings using different pooling methods (Keus 2009a), and the other evaluating the risk of random error (Keus 2009b) by using trial sequential analysis (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009).

From previous studies including simulation studies, it is known that zero event trials may introduce analytical problems (Sweeting 2004; Bradburn 2007). In our systematic review there were many zero-event trials. Therefore, we evaluated the role of different continuity corrections, summary effect measures, and statistical methods for pooling data considering outcomes on rare events, including zero event trials. In numerous robustness assessments we found important inconsistencies in inferences, confidence intervals, and pooled intervention effect estimates (Keus 2009a).

An inconsistency in conclusions was found with respect to intra-operative complications. Robustness assessments showed more intra-operative complications in the laparoscopic cholecystectomy group. However, detailed evaluation of the types of intra-operative complication causing this statistical difference showed that intra-operative gallbladder perforations were responsible for this. Many surgeons will not regard gallbladder perforations to be a complication. Therefore, overall, these robustness assessments agreed that no significant difference was found in primary outcomes (mortality and complications) between laparoscopic and small-incision cholecystectomy.

In another study, we applied trial sequential analysis to our laparoscopic versus small-incision cholecystectomy review (Keus 2009b). This technique has been developed for the evaluation of the risk of random error due to the play of chance and multiple testing in cumulative meta-analysis in order to prevent premature conclusions due to spurious findings. Analyses were restricted to the primary outcome measures. Additionally we constructed a composite outcome measure 'serious adverse events' including all important complications. Analyses were based on low bias risk estimates of control event rates and intervention effects. Furthermore, adjustments were made for the bias risks of trials as well as heterogeneity. It appeared that the information size needed for strong conclusions is not reached for mortality, bile duct injuries, and severe complications. Considering intra-operative and total complication proportions, it appeared, that intra-operative gallbladder perforations influenced the results importantly. After excluding gallbladder perforations from the analyses (for their lack of clinical relevance), the information size needed for strong conclusions was reached. No significant differences were found between laparoscopic and small-incision cholecystectomy considering intra-operative and total complications. Since the more clinical relevant question of potential differences between laparoscopic and small-incision cholecystectomy with respect to serious complications was not answered, we considered the composite outcome measure 'serious adverse events'. The information size needed to draw strong conclusions with respect to serious adverse events is within reach with one additional multicentre trial with low risk of bias. When ignoring intra-operative gallbladder perforations as a complication, all trial sequential analyses agree that so far there is no argument to support either laparoscopic or small-incision cholecystectomy.

Our two additional studies on assessments on robustness of evidence and trial sequential analyses confirm the review conclusions of no significant differences between laparoscopic and small-incision cholecystectomy considering primary outcome measures.

An issue in applicability is the question whether selection for randomised trials introduces bias so that participation is associated with greater risks and that outcomes are worse than expected in daily life practice. Differences in outcomes caused by a different (better or worse) treatment have to be distinguished from a better recording of outcomes. There is empirical evidence that participation in randomised trials does not lead to worse outcomes and that results are applicable to usual practice (Vist 2005; Vist 2008), so there seems to be no difference in treatment outcomes (Winkel 2007). Yet one could expect that through a more careful follow-up, outcomes are better recorded leading to more objective results.

The three systematic reviews report different complication proportions in both the totals and the complication categories. Complications are higher in the laparoscopic versus small-incision cholecystectomy review compared to the other two reviews. We believe that differences in methodological quality may explain these differences in data: the overall risk of bias in the laparoscopic versus small-incision cholecystectomy review was considered relatively low compared to the other two reviews. These observations are in accordance with other studies showing linkage between unclear and inadequate methodological quality to significant overestimation of beneficial effects and underreporting of adverse effects. High-quality trials are more likely to estimate the ´true´ effects of the interventions (Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008). The differences in the design of the trials may also explain differences in complications. Many trials in the laparoscopic versus open cholecystectomy review focus on haemodynamics, acute phase reactants, oxidative stress factor, or endocrine functioning etcetera. These outcomes are short-term results, implying limited follow-up. Moreover, these trials have probably not focused on complications, making registration probably less accurate. Therefore, underreporting may very well explain the lower complication proportions in the laparoscopic versus open cholecystectomy review. However, heterogeneity may be another factor explaining the differences in complication proportions. Other factors like changing practices over the years, changes in surgical techniques, or improvements in anaesthesia cannot be ruled out to play a role as well.

Based on 6 billion people in the world, an occurrence of gallstones of 5%, assuming that 10% of these people become symptomatic and that roughly 50% of symptomatic patients may undergo cholecystectomy, it can be calculated that 15 million cholecystectomies could be performed worldwide annually. The assumptions are all chosen towards the lower boundaries, so that these calculations probably underestimate the true figure. We showed in the review an average quicker operative time of 16 minutes using the small-incision approach compared with the laparoscopic operation. Accordingly, worldwide, 4 million hours operative time could potentially be saved when changing from laparoscopic to small-incision cholecystectomy annually. Now that resources are becoming more scarce, this may offer additional opportunities and solutions for other problems.

There was no significant difference in hospital stay between laparoscopic and small-incision cholecystectomy, but hospital stay was shorter in both minimally invasive techniques compared with the open cholecystectomy. One might find hospital stay long compared to daily life practice. Probably, study conditions and different practice over time are responsible. Apart from these reasons, there might be other reasons for differences in hospital stay, including cultural differences (Vitale 1991). However, we have to remember that hospital stay is only a surrogate marker for convalescence and because of numerous factors influencing its length, it does not necessary reflect objective differences between two operative procedures. Differences in hospital stay in open studies may represent bias, unless the type of surgery is blinded. Therefore, differences in hospital stay have to be interpreted with care. We feel that the importance of hospital stay is overrated in surgical literature, probably due to the fact that it can be measured so easily. The GRADE categorisation of outcomes places hospital stay in perspective to other outcomes like mortality and grades

hospital stay as being 'not important for decision making - of lower importance to patients' (Guyatt 2008a). In case two interventions do not have similar effect on patient important outcomes, length of hospital stay may, however, become important to patients and tax or insurance payers.

Outcomes not reported in the systematic reviews

Additional data are available on other outcomes including pulmonary function and analgesic use, health status, and costs. The conclusions in the individual randomised trials on these outcomes are contrasting. These outcomes were not reported in the systematic reviews and the overview of reviews due to statistical problems in meta-analysing these data as well as a lack of uniformity in the way some of these outcomes were measured. Therefore, we have summarised qualitatively the available data from the randomised trials on these outcomes.

Pulmonary function and analgesic use

Pulmonary function differences between laparoscopic and small-incision cholecystectomy have been studied in seven randomised trials (Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999; Harju 2006; Keus 2007). Since different variables and different times of measurement were chosen, outcomes were reported inconsistently (Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999; Harju 2006; Keus 2007), involved small numbers of patients (Coelho 1993; Squirrell 1998; Bruce 1999) as well as seemed to incorporate some important methodological shortcomings (Kunz 1992; Coelho 1993; Harju 2006). Three trials suggested superiority of a procedure, based upon a difference in one (Kunz 1992; Coelho 1993) or two (Bruce 1999) pulmonary function variables. Three trials incorporated sample sizes of 15 patients or less per intervention group (Coelho 1993; Squirrell 1998; Bruce 1999). Two trials used a blind approach (Squirrell 1998; Keus 2007). Details on peri-operative anaesthesia management were not provided in five of these trials (Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999). One larger trial with 64 patients in each group, found that the laparoscopic technique was superior and reported both pulmonary function testing and analgesic use (McMahon 1993; McMahon 1994). However, this multi-centre trial did not attempt to either blind patients or physicians, details on anaesthesia management were not provided, and an incision of 10 cm was considered small, ignoring the more commonly used 8 cm limitation (McMahon 1993; McMahon 1994). Harju et al evaluated pulmonary function in some of their patients (without explaining how these were selected) and found no significant difference between both techniques (Harju 2006). Our trial including 257 patients showed no significant differences evaluating eight pulmonary function variables and analgesic use (Keus 2007). Overall, qualitatively summarising the results of these seven randomised trials, we conclude that no differences in pulmonary function and analgesic use have been shown between laparoscopic and small-incision cholecystectomy.

Health status

Differences in health status between laparoscopic and small-incision cholecystectomy were examined in four trials (Barkun 1992; McMahon 1994a; Squirrell 1998; Keus 2008b). Recently, evidence-based guidelines advise to use the gastrointestinal quality of life index (GIQLI) and the short form (SF-36) for evaluating health status in cholecystectomy (Korolija 2004). Retrospectively, three (Barkun 1992; McMahon 1994a; Squirrell 1998) of the four trials did not use the appropriate questionnaires and one trial did (Keus 2008b). These questionnaires appear to be valid for evaluating patients' functional recovery after cholecystectomy (Korolija 2004). One trial with low risk of bias including 257 patients and using the appropriate questionnaires found no significant differences between laparoscopic and small-incision cholecystectomy (Keus 2008b).

Cosmetic results of both minimal-invasive results were evaluated in one trial comparing laparoscopic versus small-incision cholecystectomy (Keus 2008b). The cosmetic effect of both techniques was evaluated using the validated body image questionnaire (Dunker 1998). This low bias risk trial did not find any significant difference between laparoscopic and small-incision cholecystectomy in the 257 patients (Keus 2008b).

Costs

Differences in costs between laparoscopic and small-incision cholecystectomy were considered in seven trials (McMahon 1994a; Barkun 1995; Calvert 2000; Srivastava 2001; Secco 2002; Nilsson 2004; Keus 2009c). There are several problems in analysing and pooling cost results from different studies. First, costs are reported in different ways including different cost items. Second, different points of views are taken making comparison of studies difficult. Generally, a societal perspective is recommended (Siegel 1997; Oostenbrink 2002). Third, there is a difference in validity of cost assessments, defined by the details in which costs are calculated. More detailed analyses provide more reliable estimates (Graves 2002). Fourth, there may be considerable differences in local costs. Specific items in cost analyses differ from one country or even setting to another. Fifth, cultural differences are probably the most important problem. There are wide variations in convalescence (and return to work) between different cultures depending on a multitude of causes, like social security and cultural habits (Vitale 1991). These multiple factors cause heterogeneity, and pooling results seems, therefore, inappropriate. So far, seven trials measured costs, and several of these trials had high risk of bias (McMahon 1994a; Barkun 1995; Srivastava 2001; Secco 2002). In some trials methodology of cost assessment was very limited described (McMahon 1994a; Srivastava 2001). Outpatients' costs (Calvert 2000; McMahon 1994a) and indirect costs (McMahon 1994a; Barkun 1995; Calvert 2000; Secco 2002) were excluded in several studies making overall (societal) comparison of techniques incomplete. Retrospective analyses (Secco 2002) or expert settings (Calvert 2000; Secco 2002) raise questions on reliability and generalisability. In one trial, a significant advantage was found favouring small-incision cholecystectomy with surgical residents performing 86% of the operations (Keus 2008c). Overall, the trials showed a neutral or beneficial effect favouring the small-incision technique (McMahon 1994a; Barkun 1995; Calvert 2000; Srivastava 2001; Secco 2002; Nilsson 2004), and especially, the trials with low risk of bias favoured the small-incision technique (Calvert 2000; Nilsson 2004; Keus 2008c). Qualitatively summarising cost results from the randomised trials we conclude that costs seem to be lower using small-incision cholecystectomy. Moreover, taking into account that our review did not find any significant differences between laparoscopic and small-incision cholecystectomy with respect to hospital stay and convalescence, it is even more likely that costs are lower using the small-incision approach.

Today with increasing budget restrictions we have to focus on the resource use associated with the available techniques. Savings, from an operation theatre perspective, have been reported as high as 23% when using the small-incision cholecystectomy technique. Reminding that cholecystectomy is one of the most frequently performed surgical procedures, saving resources by switching the technique of cholecystectomy offers opportunities for a re-allocation of these saved resources.

Symptom relief

Remarkably, very little to no information was available with respect to symptom relief. It seems logical that no recurrences of symptoms of gallbladder colic are to be expected when the gallbladder is removed. Especially when two different techniques for cholecystectomy are being compared, no differences in symptom relief are to be expected. However, data from lower level of evidence suggest that in up to 40% of patients, symptoms recur after cholecystectomy. Since this lower level of evidence is the best we have, the true figure remains unknown. Retrospectively, the diagnosis symptomatic cholecystectomy and the indication for cholecystectomy may not have been correct in these patients. Therefore, symptom relief should become the focus of research. Moreover, remembering the high complication proportions, it is very hard to justify the risks patients with incorrect diagnosis of symptomatic cholecystolithiasis and patients exposed to cholecystectomy with its unacceptable high complication rates are facing. Future research urgently needs to refocus on outcomes critical for decision making, ie, lowering the numbers of complications as well as achieving improvements in the accuracy of the diagnosis of symptomatic cholecystolithiasis.

Quality of the evidence

Trials with low risks of bias seem more likely to show no effect or a negative effect of laparoscopic surgery, whereas trials with high risk of bias seem more likely to show a positive effect or no effect of laparoscopic surgery. These observations are in accordance with other studies showing linkage between high risk of bias to significant overestimation of beneficial effects and underreporting of adverse effects. Trials with low risk of bias are more likely to estimate the ´true´ effects of the interventions (Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008). This overestimation of beneficial effects associated with laparoscopic surgery in trials with unclear or inadequate methodology may be an illustration of personal preferences of surgeons. Lack of objectivity biases results. Therefore, overall improvement of methodological quality of trials, and hence risk of bias, especially in surgery, is needed to obtain valid and reliable results.

We only based our assessment of bias on generation of the allocation sequence, allocation concealment, blinding, and follow-up. It is a weakness that we have not assessed bias due to selective outcome reporting, baseline differences, early stopping, and vested interests (Higgins 2008; Gluud 2009). We plan to address these issues in future updates of the reviews.

Potential biases in the overview process

The first and most important potential source of bias relates to us, being the authors of all the three included Cochrane reviews. Additionally, we performed one of the trials with low risk of bias. We might not have recognised the potential mistakes conducted in the review process, neither may we be aware of any other potential sources of bias present in the three included reviews. In contrast, having critically appraised all individual trials, we are in detail informed on their weaknesses and strengths on which the reviews build. This may be an advantage.

A second issue are the risks of bias in the included trials. A systematic review summarises results of individual trials and collects their data into pooled effect estimates. The risks of bias are assessed to evaluate the validity of the intervention effects. Obviously, a review depends on the methodological quality of the individual trials and is never capable of increasing the strength of the trials with high risks of bias. In the third comparison, laparoscopic versus small-incision cholecystectomy, the overall risk of bias was considered relatively low, while in the other two comparisons the overall risk of bias in the included trials was considered high. Therefore, the estimates of both minimal invasive techniques compared with the open technique may not be reliable estimates of the true intervention effects.

Agreements and disagreements with other studies or reviews

The total complication proportions we found in the laparoscopic versus the small-incision cholecystectomy comparison are 26.6% and 22.9%, respectively. These figures include gallbladder perforations. As some surgeons may not regard gallbladder perforation as a complication, our figures decrease to 17.0% and 17.5% if gallbladder perforation is excluded from our figures. However, these figures are still much higher than total complication figures up to 5% reported in other series and reviews including non-randomised series. Such studies represent lower levels of evidence (Southern Surgeons Club 1991; Litwin 1992; Deveney 1993; Deziel 1994; Downs 1996). We are not aware of the exact reasons for the three times higher proportion of complications reported in randomised trials as compared to that originating from observational studies, but our findings are in accordance with previous observations (Papanikolaou 2006). These observations point collectively to the fact that observational studies are more conservative than the randomised trial when reporting harm.

In the laparoscopic versus open cholecystectomy review, we found total complication proportions of 5.4% and 10.1%, respectively, with no significant difference applying the random-effects model. These figures differ from the laparoscopic versus small-incision cholecystectomy review (17.0% versus 17.5%). Probably differences in methodological quality of the trials may play a role. As results from high quality trials are more reliable (Schulz 1995; Wood 2008), we believe that the 17% is closer to the truth, particularly because the proportion of trials with low risk of bias in the laparoscopic versus small-incision cholecystectomy review outweighs the proportion of trials with low risk of bias in the laparoscopic versus open cholecystectomy review. The same arguments hold regarding the 17.5% complication proportion in small-incision cholecystectomy when compared to complication proportions in the small-incision versus open cholecystectomy review.

AUTHORS' CONCLUSIONS

Implications for practice

Both small-incision and laparoscopic cholecystectomy seem superior to open cholecystectomy. The question today is why the laparoscopic cholecystectomy has become the standard treatment of cholecystectomy for patients with symptomatic cholecystolithiasis without strong evidence showing it is superior to small-incision cholecystectomy. We were unable to identify any outcome measure, significantly and convincingly in favour of the laparoscopic approach. There are no significant differences in mortality, complications, conversions, hospital stay, and convalescence on the low risk of bias evidence level. Other outcomes not suitable for pooling in meta-analyses, like pulmonary function, pain and analgesic use, and health status were not significantly different either. Operative time and costs were significantly different, both favouring the small-incision technique. From a patient-relevant outcomes perspective, both techniques may be considered equally effective. However, from a society perspective there seem to be advantages using the small-incision technique.

The high complication proportions observed in all three techniques in trials with low risk of bias raise questions and demand for ´best practice´ standardised technical guidelines for safer cholecystectomy procedures.

Implications for research

Research should concentrate on outcomes that are relevant to patients instead of focusing on outcomes that are of interest mainly to the surgeons. The causes of the high complication proportions need to be addressed. Furthermore, one additional trial with low risk of bias on a composite outcome measure 'serious adverse events' seems to be able to reach the cumulative information size needed for firm conclusions regarding the comparison small-incision versus laparoscopic cholecystectomy. Instead of considering total complications, which is a composite outcome measure, it may be more relevant to consider the individual complication categories since they may differ regarding their consequences to the patients. A number of the included trials did not report the specific subgroup of complications and their severity. Adverse event reporting is an issue that needs urgent attention in surgical trials. More elaborate cost evaluations, especially on a macro-economic level may provide additional arguments to decide on preferences for either one of both these techniques.

Reports on postoperative symptom relief are highly needed. The high failure rates of symptom relief suggested by lower level evidence raise questions on our quality of care. The lack of high quality evidence considering this patient relevant outcome is remarkable. We need a higher level of evidence to confirm or reject these failure rates. We urge trialists to conduct long-term follow-up to assess patient-relevant outcomes. If the figures originating from lower level of evidence appear to be true, then research should focus on improvements in the diagnostic process.

The high complication proportions in elective minimal invasive cholecystectomy should be our major concern. Today, research in surgery focuses on the widespread implementation of laparoscopy rather than improving critical patient relevant outcomes. We ought to worry about the patients' interests and take their perspective when considering a hierarchy of relevance of outcomes as recommended by the GRADE Working Group (Guyatt 2008a). It is worrying that we focus on reducing hospital stay by implementing laparoscopic surgery rather than focusing on critical patient relevant outcomes.

The overall quality of the included randomised trials varied with the majority of trials having several methodological deficiencies. The quality of trials needs to improve by adopting the CONSORT Statement (www.consort-statement.org).

There are several questions that still remain unanswered, like questions regarding pulmonary consequences after surgery, cost aspects, and more detailed questions on convalescence.

ACKNOWLEDGEMENTS

We thank Christian Gluud for useful comments and advice and The Cochrane Hepato-Biliary Review Group, Copenhagen, for excellent support. We thank all our coworkers on previous studies on cholecystectomy for excellent collaboration.

REFERENCES

References to included reviews

Keus 2006a

Keus F, de Jong J, Gooszen HG, Laarhoven CJHM. Small-incision versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD004788.pub2]

Keus 2006b

Keus F, de Jong J, Gooszen HG, Laarhoven CJHM. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD006231]

Keus 2006c

Keus F, de Jong J, Gooszen HG, van Laarhoven CHJM. Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD006229]

Additional references

Atkins 2004

Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. The GRADE Working Group. *BMC Health Services Research* 2004;**4**(1):38.

Atkins 2005

Atkins D, Briss PA, Eccles M, Flottorp S, Guyatt GH, Harbour RT, et al. Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system. *BMC Health Services Research* 2005;**5**(1):25.

Attili 1995

Attili AF, Carulli N, Roda E, Barbara B, Capocaccia L, Menotti A, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). *American Journal of Epidemiology* 1995;**141**(2):158-65. [PUBMED: 7817971]

Barkun 1992

Barkun JS, Barkun AN, Sampalis JS, Fried G, Taylor B, Wexler MJ, et al. Randomised controlled trial of laparoscopic versus mini cholecystectomy. The McGill Gallstone Treatment Group. *Lancet* 1992;**340**(8828):1116-9. [PUBMED: 1359210]

Barkun 1995

Barkun JS, Caro JJ, Barkun AN, Trindade E. Cost-effectiveness of laparoscopic and mini-cholecystectomy in a prospective randomized trial. *Surgical Endoscopy* 1995;**9**(11):1221-4. [PUBMED: 8553241]

Bradburn 2007

Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in Medicine* 2007;**26**(1):53-77.

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**(8):763-9. [PUBMED: 18411040]

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287-98. [PUBMED: 18824466]

Bruce 1999

Bruce DM, Smith M, Walker CB, Heys SD, Binnie NR, Gough DB, et al. Minimal access surgery for cholelithiasis induces an attenuated acute phase response. *American Journal of Surgery* 1999;**178**(3):232-4. [PUBMED: 10527445]

Calvert 2000

Calvert NW, Troy GP, Johnson AG. Laparoscopic cholecystectomy: a good buy? A cost comparison with small-incision (mini) cholecystectomy. *The European Journal of Surgery* 2000;**166**(10):782-6. [PUBMED: 11071165]

Coelho 1993

Coelho JC, de Araujo RP, Marchesini JB, Coelho IC, de Araujo LR. Pulmonary function after cholecystectomy performed through Kocher's incision, a mini-incision, and laparoscopy. *World Journal of Surgery* 1993;**17**(4):544-6. [PUBMED: 8362533]

Deveney 1993

Deveney KE. The early experience with laparoscopic cholecystectomy in Oregon. *Archives of Surgery (Chicago, Ill.: 1960)* 1993;**128**(6):627-32. [PUBMED: 8503764]

Deziel 1993

Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko ST, Airan MC. Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. *American Journal of Surgery* 1993;**165**(1):9-14. [PUBMED: 8418705]

Deziel 1994

Deziel DJ. Complications of cholecystectomy. Incidence, clinical manifestations, and diagnosis. *The Surgical Clinics of North America* 1994;**74**(4):809-23. [PUBMED: 8047943]

Downs 1996

Downs SH, Black NA, Devlin HB, Royston CM, Russell RC. Systematic review of the effectiveness and safety of laparoscopic cholecystectomy. *Annals of the Royal College of Surgeons of England* 1996;**78**(3 part II):241-323.

Dubois 1982

Dubois F, Berthelot B. Cholecystectomy through minimal incision (author's translation) [Cholecystectomie par mini-laparotomie]. *La Nouvelle Presse Medicale* 1982;**11**(15):1139-41. [PUBMED: 7079137]

Dunker 1998

Dunker MS, Stiggelbout AM, van Hogezand RA, Ringers J, Griffioen G, Bemelman WA. Cosmesis and body image after laparoscopic-assisted and open ileocolic resection for Crohn's disease. *Surgical Endoscopy* 1998;**12**:1334-40.

Egger 2003

Egger M, Davey SG, Schneider M, Binder C. Bias in meta-analysis detected by a simple, graphical test. *Health Technology Assessment* 2003;**7**(1):1-76.

Everhart 1999

Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999;**117**(3):632-9. [PUBMED: 10464139]

Gluud 2009

Gluud C, Nikolova D, Klingenberg SL, Alexakis N, Als-Nielsen B, Colli A, et al. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)). 2009, Issue 4. Art. No.: LIVER.

Goco 1983

Goco IR, Chambers LG. "Mini-cholecystectomy" and operative cholangiography. A means of cost containment. *The American Surgeon* 1983;**49**(3):143-5. [PUBMED: 6830067]

Graves 2002

Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Economics* 2002;**11**(8):735-9. [PUBMED: 12457373]

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical Research Ed.)* 2008;**336**(7650):924-6.

Guyatt 2008a

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ (Clinical Research Ed.)* 2008;**336**(7651):995-8.

Harju 2006

Harju J, Juvonen P, Eskelinen M, Miettinen P, Paakkonen M. Minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a randomized study with special reference to obesity. *Surgical Endoscopy* 2006;**20**(4):583-6. [PUBMED: 16437283]

Higgins 2006

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 4.2.6 [updated September 2006]. The Cochrane Collaboration, 2006. Available from www.cochrane-handbook.org.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Jensen 1991

Jensen KH, Jorgensen T. Incidence of gallstones in a Danish population. *Gastroenterology* 1991;**100**(3):790-4. [PUBMED: 1993501]

Johnston 1993

Johnston DE, Kaplan MM. Pathogenesis and treatment of gallstones. *The New England Journal of Medicine* 1993;**328**(6):412-21. [PUBMED: 8421460]

Jüni 2001

Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ (Clinical research ed.)* 2001;**323**(7303):42-6. [PUBMED: 11440947]

Keus 2007

Keus F, Ahmed Ali U, Noordergraaf GJ, Roukema JA, Gooszen HG, van Laarhoven CJ. Anaesthesiological considerations in small-incision and laparoscopic cholecystectomy in symptomatic cholecystolithiasis: implications for pulmonary function. A randomized clinical trial. *Acta Anaesthesiologica Scandinavica* 2007;**51**(8):1068-78. [PUBMED: 17697302]

Keus 2008a

Keus F, Gooszen HG, van Laarhoven CJ. Systematic review: Cochrane Hepato-Biliary Group systematic review of randomized clinical trials: open, small-incision, or laparoscopic cholecystectomy for symptomatic cholecystolithiasis. *Alimentary Pharmacology & Therapeutics* 2009;**29**(4):359-78. [PUBMED: 19035965]

Keus 2008b

Keus F, de Vries J, Gooszen HG, van Laarhoven CJ. Laparoscopic versus small-incision cholecystectomy: health status in a blind randomised trial. *Surgical Endoscopy* 2008;**22**(7):1649-59. [PUBMED: 18071815]

Keus 2008c

Keus F, Werner JE, Gooszen HG, Oostvogel HJ, van Laarhoven CJ. Randomized clinical trial of small-incision and laparoscopic cholecystectomy in patients with symptomatic cholecystolithiasis: primary and clinical outcomes. *Archives of Surgery (Chicago, Ill.: 1960)* 2008;**143**(4):371-7; discussion 377-8. [PUBMED: 18427025]

Keus 2009a

Keus F, Wetterslev J, Gluud C, Gooszen HG, van Laarhoven CJHM. Robustness assessments are needed to

reduce bias in meta-analyses including zero-event randomized trials. *American Journal of Gastroenterology* 2009;**104(3)**:546-51.

Keus 2009b

Keus F, Wetterslev J, Gluud C, Gooszen HG, van Laarhoven CJHM. Trial sequential analyses of meta-analyses of complications in laparoscopic versus small-incision cholecystectomy. *Journal of Clinical Epidemiology* 2009;**in press**:doi:10.1016/j.jclinepi.2009.08.023 .

Keus 2009c

Keus F, de Jonge T, Gooszen HG, Buskens E, van Laarhoven CJHM. Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective: sick leave outweighs efforts in hospital savings. *Trials* 2009;**10**:80.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9. [PUBMED: 11730399]

Korolija 2004

Korolija D, Sauerland S, Wood-Dauphinee S, Abbou CC, Eypasch E, Caballero MG, et al. Evaluation of quality of life after laparoscopic surgery: evidence-based guidelines of the European Association for Endoscopic Surgery. *Surgical Endoscopy* 2004;**18**(6):879-97. [PUBMED: 15108103]

Kunz 1992

Kunz R, Orth K, Vogel J, Steinacker JM, Meitinger A, Bruckner U, et al. Laparoscopic cholecystectomy versus mini-lap-cholecystectomy. Results of a prospective, randomized study [Laparoskopische Cholecystektomie versus Mini-Lap-Cholecystektomie. Ergebnisse einer prospektiven, randomisierten Studie.]. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen* 1992;**63**(4):291-5. [PUBMED: 1534528]

Ledet 1990

Ledet WP Jr. Ambulatory cholecystectomy without disability. *Archives of Surgery (Chicago, Ill.: 1960)* 1990;**125**(11):1434-5. [PUBMED: 2241552]

Legorreta 1993

Legorreta AP, Silber JH, Costantino GN, Kobylinski RW, Zatz SL. Increased cholecystectomy rate after the introduction of laparoscopic cholecystectomy. *Journal of the American Medical Association* 1993;**270**(12):1429-32. [PUBMED: 8371441]

Litwin 1992

Litwin DE, Girotti MJ, Poulin EC, Mamazza J, Nagy AG. Laparoscopic cholecystectomy: trans-Canada experience with 2201 cases. *Canadian Journal of Surgery. Journal Canadien de Chirurgie* 1992;**35**(3):291-6. [PUBMED: 1535548]

McMahon 1993

McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ. Ventilatory and blood gas changes during laparoscopic and open cholecystectomy. *The British Journal of Surgery* 1993;**80**(10):1252-4. [PUBMED: 8242290]

McMahon 1994

McMahon AJ, Russell IT, Ramsay G, Sunderland G, Baxter JN, Anderson JR, et al. Laparoscopic and minilaparotomy cholecystectomy: a randomized trial comparing postoperative pain and pulmonary function. *Surgery* 1994;**115**(5):533-9. [PUBMED: 8178250]

McMahon 1994a

McMahon AJ, Russell IT, Baxter JN, Ross S, Anderson JR, Morran CG, et al. Laparoscopic versus minilaparotomy cholecystectomy: a randomised trial. *Lancet* 1994;**343**(8890):135-8. [PUBMED: 7904002]

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13. [PUBMED: 9746022]

Mühe 1986

Mühe E. The first cholecystectomy by laparoscope [Die erste Cholecystektomie durch das Laparoskop]. *Langenbecks Archiv für Chirurgie* 1986;**369**:804.

Neugebauer 1995

Neugebauer E, Troidl H, Kum CK, Eypasch E, Miserez M, Paul A. The E.A.E.S. Consensus Development Conferences on laparoscopic cholecystectomy, appendectomy, and hernia repair. Consensus statements--September 1994. The Educational Committee of the European Association for Endoscopic Surgery. *Surgical Endoscopy* 1995;**9**(5):550-63. [PUBMED: 7676385]

NIH Consensus conference 1993

NIH Consensus conference. Gallstones and laparoscopic cholecystectomy. *Journal of the American Medical Association* 1993;**269**(8):1018-24. [PUBMED: 8429583]

Nilsson 2004

Nilsson E, Ros A, Rahmqvist M, Backman K, Carlsson P. Cholecystectomy: costs and health-related quality of life: a comparison of two techniques. *International Journal for Quality in Health Care* 2004;**16**(6):473-82. [PUBMED: 15557357]

O'Dwyer 1990

O'Dwyer PJ, Murphy JJ, O'Higgins NJ. Cholecystectomy through a 5 cm subcostal incision. *The British Journal of Surgery* 1990;**77**(10):1189-90. [PUBMED: 2224473]

Olsen 1991

Olsen DO. Laparoscopic cholecystectomy. *American Journal of Surgery* 1991;**161**(3):339-44. [PUBMED: 1825754]

Olsen 1993

Olsen DO. Mini-lap cholecystectomy. *American Journal of Surgery* 1993;**165**(4):440-3. [PUBMED: 8480878]

Oostenbrink 2002

Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *PharmacoEconomics* 2002;**20**(7):443-54. [PUBMED: 12093300]

Papanikolaou 2006

Papanikolaou PN, Christidi GD, Ioannidis JPA. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *Canadian Medical Association Journal* 2006;**174**(5):635-41. [10.1503/cmaj.050873]

Roslyn 1993

Roslyn JJ, Binns GS, Hughes EF, Saunders-Kirkwood K, Zinner MJ, Cates JA. Open cholecystectomy. A contemporary analysis of 42,474 patients. *Annals of Surgery* 1993;**218**(2):129-37. [PUBMED: 8342992]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**(5):408-12. [PUBMED: 7823387]

Scott 1992

Scott EA, Black N. Appropriateness of cholecystectomy: the public and private sectors compared. *Annals of the Royal College of Surgeons of England* 1992;**74**(4 Suppl):97-101. [PUBMED: 1416696]

Seale 1999

Seale AK, Ledet WP Jr. Minicholecystectomy: a safe, cost-effective day surgery procedure. *Archives of Surgery (Chicago, Ill.: 1960)* 1999;**134**(3):308-10. [PUBMED: 10088574]

Secco 2002

Secco GB, Cataletti M, Bonfante P, Baldi E, Davini MD, Biasotti B, et al. Laparoscopic versus mini-cholecystectomy: analysis of hospital costs and social costs in a prospective randomized study [Video-colecistectomia versus mini-colecistectomia: analisi dei costi ospedalieri e dei costi sociali in uno studio prospettico randomizzato]. *Chirurgia Italiana* 2002;**54**(5):685-92. [PUBMED: 12469466]

Shea 1996

Shea JA, Healey MJ, Berlin JA, Clarke JR, Malet PF, Staroscik RN, et al. Mortality and complications associated with laparoscopic cholecystectomy. A meta-analysis. *Annals of Surgery* 1996;**224**(5):609-20. [PUBMED: 8916876]

Siegel 1997

Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. *PharmacoEconomics* 1997;**11**(2):159-68. [PUBMED: 10172935]

Southern Surgeons Club 1991

The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. *The New England Journal of Medicine* 1991;**324**(16):1073-8. [PUBMED: 1826143]

Squirrell 1998

Squirrell DM, Majeed AW, Troy G, Peacock JE, Nicholl JP, Johnson AG. A randomized, prospective, blinded comparison of postoperative pain, metabolic response, and perceived health after laparoscopic and small incision cholecystectomy. *Surgery* 1998;**123**(5):485-95. [PUBMED: 9591000]

Srivastava 2001

Srivastava A, Srinivas G, Misra MC, Pandav CS, Seenu V, Goyal A. Cost-effectiveness analysis of laparoscopic versus minilaparotomy cholecystectomy for gallstone disease. A randomized trial. *International Journal of Technology Assessment in Health Care* 2001;**17**(4):497-502. [PUBMED: 11758294]

Steiner 1994

Steiner CA, Bass EB, Talamini MA, Pitt HA, Steinberg EP. Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. *The New England Journal of Medicine* 1994;**330**(6):403-8. [PUBMED: 8284007]

Sweeting 2004

Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Satistics in Medicine* 2004;**23**(9):1351-75.

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses?. *International Journal of Epidemiology* 2009;**38**(1):276-86. [PUBMED: 18824467]

Traverso 1976

Traverso LW. Carl Langenbuch and the first cholecystectomy. *American Journal of Surgery* 1976;**132**(1):81-2. [PUBMED: 782269]

Tyagi 1994

Tyagi NS, Meredith MC, Lumb JC, Cacdac RG, Vanterpool CC, Rayls KR, et al. A new minimally invasive technique for cholecystectomy. Subxiphoid "minimal stress triangle": microceliotomy. *Annals of Surgery* 1994;**220**(5):617-25. [PUBMED: 7979609]

Vist 2005

Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *BMJ (Clinical Research Ed.)* 2005;**330**(7501):1175. [PUBMED: 15905256]

Vist 2008

Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD. Outcomes of patients who participate in randomised controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.MR000009.pub4]

Vitale 1991

Vitale GC, Collet D, Larson GM, Cheadle WG, Miller FB, Perissat J. Interruption of professional and home activity after laparoscopic cholecystectomy among French and American

patients. *American Journal of Surgery* 1991;**161**(3):396-8. [PUBMED: 1825766]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [PUBMED: 18083463]

Winkel 2007

Winkel P. Statistical Development of Quality in Medicine. John Wiley & Sons, Inc., 2007.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5.

ADDITIONAL TABLES

Table 1. Search strategy

Database	Search performed in	Search strategy
The Cochrane Database of Systematic Reviews (CDSR)	Issue 4, 2009	'cholecystectomy'

Table 2. Characteristics of included reviews

Review	Date assessed as up to date	Population	Interventions	Comparison interventions	Outcomes for which data were reported	Review limitations
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Small-incision cholecystectomy	Open cholecystectomy	Primary: complications Secondary: operative time, hospital stay	Systematic error: the included trials had relatively low methodological quality Random error: only 7 trials including 572 patients were included Time: the review needs updating
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Laparoscopic cholecystectomy	Open cholecystectomy	Primary: mortality, complications Secondary: operative time, hospital stay, convalescence	Systematic error: the included trials had relatively low methodological quality Time: the review needs updating
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Laparoscopic cholecystectomy	Small-incision cholecystectomy	Primary: mortality, complications Secondary: conversions, operative time, hospital stay, convalescence	Time: the review needs updating

Table 3. Overview of primary outcomes: numbers of included patients and trials

Review		Mortality	Intra-operative complications	Minor complications	Severe complications	Bile duct injuries	Total complications
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	0 (0)	571 (7)	571 (7)	571 (7)	571 (7)	571 (7)
	Trials with low risk of bias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	987 (15)	1914 (30)	1914 (30)	1914 (30)	1914 (30)	1914 (30)
	Trials with low risk of bias	0 (0)	63 (2)	63 (2)	63 (2)	63 (2)	63 (2)
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	1952 (7)	2315 (12)	2315 (12)	2315 (12)	2315 (12)	2315 (12)
	Trials with low risk of bias	1181 (3)	1181 (3)	1181 (3)	1181 (3)	1181 (3)	1181 (3)

The three rows represent the three included reviews. The outcomes are in the columns, including all patients and all trials and separately for the trials with low risk of bias. The numbers in the columns are the numbers of randomised patients with the numbers of trials reporting that outcome in brackets.

Table 4. Overview of secondary outcomes: numbers of included patients and trials

Review		Conversions	Convalescence: work leave (days)	Convalescence: normal activity (days)	Operative time (minutes)	Hospital stay (days)
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	n.a.	0 (0)	0 (0)	210 (3)	180 (2)
	Trials with low risk of bias	n.a.	0 (0)	0 (0)	0 (0)	0 (0)
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	n.a.	328 (3)	0 (0)	1134 (24)	1111 (21)
	Trials with low risk of bias	n.a.	0 (0)	0 (0)	20 (1)	20 (1)
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	2132 (8)	1181 (3)	1158 (4)	1953 (9)	1614 (8)
	Trials with low risk of bias	1181 (3)	1181 (3)	924 (2)	1181 (3)	1181 (3)

The three rows represent the three included reviews. The outcomes are in the columns, including all patients and all trials and separately for the trials with low risk of bias.
The numbers in the columns are the numbers of randomised patients with the numbers of trials reporting that outcome in brackets.

Table 5. Summary of Findings table: OC vs SIC

		Quality assessment				Summary of findings				
Outcomes		**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	***Risk OC (control)***	***Risk SIC (comparator)***	**Relative effect - SIC vs OC**	**Absolute effect - SIC vs OC**	**Quality of the evidence (GRADE)**
Intra-operative complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	0 per 279 (0%)	0 per 292 (0%)	not estimable	0 more per 1000	VERY LOW
Minor complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	19 per 279 (6.8%)	25 per 292 (8.6%)	1.26	18 more per 1000	VERY LOW
Severe complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	7 per 279 (2.5%)	4 per 292 (1.4%)	0.56	11 fewer per 1000	VERY LOW
Bile duct injuries	All trials	very serious	serious	no serious indirectness	serious	none	0 per 279 (0%)	0 per 292 (0%)	not estimable	0 fewer per 1000	VERY LOW
Total complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	26 per 279 (9.3%)	29 per 292 (9.9%)	1.06	6 more per 1000	VERY LOW

Modified table using GRADE pro software.
OC: open cholecystectomy;
SIC: small-incision cholecystectomy;
RR: relative risk
GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of five factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias. Upgrading of evidence (increase quality of evidence) may occur based on the assessment of three factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

Table 6. Summary of Findings table: OC vs LC

		Quality assessment				Summary of findings				
Outcomes		**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	***Risk OC (control)***	***Risk LC (comparator)***	**Relative effect - LC vs OC**	**Absolute effect - LC vs OC**	**Quality of the evidence (GRADE)**
Mortality	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	1 per 485 (0.2%)	0 per 502 (0%)	not estimable	2 fewer per 1000	VERY LOW
Intra-operative complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	1 per 939 (0.1%)	9 per 975 (0.9%)	9.0	8 more per 1000	VERY LOW
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	0 per 32 (0%)	0 per 31 (0%)	not estimable	0 more per 1000	LOW
Minor complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	35 per 939 (3.7%)	23 per 975 (2.4%)	0.65	13 fewer per 1000	VERY LOW
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	1 per 32 (3.1%)	0 per 31 (0%)	not estimable	31 fewer per 1000	LOW
Severe complications	All trials	very serious	serious	no serious indirectness	serious	none	72 per 939 (7.7%)	25 per 975 (2.6%)	0.34	51 fewer per 1000	VERY LOW
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	1 per 32 (3.1%)	0 per 31 (0%)	not estimable	31 fewer per 1000	LOW

Table 6. Summary of Findings table: OC vs LC *(Continued)*

Bile duct injuries	All trials	very serious	serious	no serious indirectness	serious	none	2 per 939 (0.2%)	2 per 975 (0.2%)	1.0	0 fewer per 1000	VERY LOW
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	very serious	none	0 per 32 (0%)	0 per 31 (0%)	not estimable	0 fewer per 1000	VERY LOW
Total complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	110 per 939 (11.7%)	59 per 975 (6.1%)	0.52	56 fewer per 1000	VERY LOW
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	2 per 32 (6.3%)	0 per 31 (0%)	not estimable	63 fewer per 1000	LOW

Modified table using GRADE pro software. OC: open cholecystectomy; LC: laparoscopic cholecystectomy; RR: relative risk
GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of 5 factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias. Upgrading of evidence (increase quality of evidence) may occur based on the assessment of 3 factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

Table 7. Summary of Findings table: LC vs SIC

		Quality assessment				Summary of findings					
Outcomes		**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	***Risk SIC (control)***	***Risk LC (comparator)***	**Relative effect - LC vs SIC**	**Absolute effect - LC vs SIC**	**Quality of the evidence (GRADE)**
Mortality	All trials	serious	no serious inconsistency	no serious indirectness	serious	none	1 per 977	1 per 975	1.00	0 fewer per 1000	LOW

Table 7. Summary of Findings table: LC vs SIC *(Continued)*

						(0.1%)	(0.1%)			
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	serious	none0 per 599 (0%)	0 per 582 (0%)	not estimable	0 fewer per 1000	MODERATE
Intra-operative complications	All trials	very serious	very serious	no serious indirectness	serious	none88 per 1151 (7.6%)	153 per 1164 (13.1%)	1.72	55 more per 1000	VERY LOW
	Trials with low risk of bias	no serious limitations	serious	no serious indirectness	no serious imprecision	none87 per 599 (14.5%)	153 per 582 (26.3%)	1.81	118 more per 1000	MODERATE
minor complications	All trials	serious	serious	no serious indirectness	serious	none106 per 1151 (9.2%)	97 per 1164 (8.3%)	0.90	9 fewer per 1000	VERY LOW
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none58 per 599 (9.7%)	57 per 582 (9.8%)	1.01	1 more per 1000	HIGH
Severe complications	All trials	serious	serious	no serious indirectness	no serious imprecision	none48 per 1151 (4.2%)	46 per 1164 (4.0%)	0.95	2 fewer per 1000	LOW
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none34 per 599 (5.7%)	27 per 582 (4.6%)	0.81	11 fewer per 1000	HIGH
Bile duct injuries	All trials	serious	serious	no serious indirectness	serious	none22 per 1151 (1.9%)	14 per 1164 (1.2%)	0.63	6 fewer per 1000	VERY LOW
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	serious	none10 per 599 (1.7%)	8 per 582 (1.4%)	0.82	3 fewer per 1000	MODERATE
Total com-	All trials	serious	very serious	no serious indirectness	no serious imprecision	none264 per 1151	310 per 1164	1.16	37 more per 1000	VERY LOW

Table 7. Summary of Findings table: LC vs SIC *(Continued)*

plica-tions							(22.9%)	(26.6%)		
	Trials with low risk of bias	no serious limitations	no serious in-consistency	no serious indi-rectness	no serious imprecision	none	189 per 599 (31.6%)	245 per 582 (42.1%)	1.33	105 more per 1000	HIGH

Modified table using GRADE pro software.
LC: laparoscopic cholecystectomy;
SIC: small-incision cholecystectomy;
RR: relative risk
GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of 5 factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias. Upgrading of evidence (increase quality of evidence) may occur based on the assessment of 3 factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

WHAT'S NEW

Date	Event	Description
29 December 2009	Amended	Search strategy table added.

CONTRIBUTIONS OF AUTHORS

F Keus, HG Gooszen, and CJHM van Laarhoven prepared this overview of reviews.

DECLARATIONS OF INTEREST

The authors of this overview also conducted all the three included systematic reviews. Additionally, the authors also conducted one of the trials with low risk of bias on laparoscopic versus small-incision cholecystectomy.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholecystectomy [adverse effects] [*methods]; Cholecystectomy, Laparoscopic [adverse effects] [methods]; Cholecystolithiasis [*surgery]; Outcome Assessment, Health Care; Randomized Controlled Trials as Topic

MeSH check words

Humans