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Cholecystectomy for patients with silent gallstones (Review)

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[Intervention Review]

Cholecystectomy for patients with silent gallstones

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ABSTRACT

Background

Cholecystectomy is currently advised only for patients with symptomatic gallstones. However, about 4% of patients with asymptomatic gallstones develop symptoms including cholecystitis, obstructive jaundice, pancreatitis, and gallbladder cancer.

Objectives

To assess the benefits and harms of surgical removal of the gallbladder for patients with asymptomatic gallstones.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE,* and *Science Citation Index Expanded* until May 2008.

Selection criteria

Only randomised clinical trials (irrespective of language, blinding, or publication status) comparing cholecystectomy and no cholecystectomy were considered for the review.

Data collection and analysis

We were unable to identify any randomised clinical trials comparing cholecystectomy versus no cholecystectomy.

Main results

We were unable to identify any randomised clinical trial comparing cholecystectomy versus no cholecystectomy.

Authors' conclusions

There are no randomised trials comparing cholecystectomy versus no cholecystectomy in patients with silent gallstones. Further evaluation of observational studies, which measure outcomes such as obstructive jaundice, gallstone-associated pancreatitis, and/or gall-bladder cancer for sufficient duration of follow-up is necessary before randomised trials are designed in order to evaluate whether cholecystectomy or no cholecystectomy is better for asymptomatic gallstones.

PLAIN LANGUAGE SUMMARY

No evidence to assess surgical treatment in asymptomatic gallstones

Cholecystectomy is currently advised only for symptomatic gallstones. However, about 4% of patients with asymptomatic gallstones develop symptoms including cholecystitis, obstructive jaundice, pancreatitis, and gallbladder cancer. Literature search was performed for evidence from randomised clinical trials to find whether cholecystectomy was indicated in patients with silent (asymptomatic) gallstones. There is no randomised trial comparing cholecystectomy versus no cholecystectomy in silent gallstones. Further evaluation of observational studies, which measure outcomes such as obstructive jaundice, gallstone-associated pancreatitis, and/or gall-bladder cancer for sufficient duration of follow-up is necessary before randomised trials are designed in order to evaluate whether cholecystectomy or no cholecystectomy is better for asymptomatic gallstones.

BACKGROUND

About 10% to 15% of the adult western population have gallstones (NIH 1992; Halldestam 2004). The annual incidence of gallstones is about 1 in 200 people (NIH 1992). Only 1% to 4% of people with gallstones become symptomatic in a year (NIH 1992; Halldestam 2004). The reported incidence of common bile duct stones at the time of cholecystectomy varies between 5% (Kama 2001; Hemli 2004) and 11% (Pitluk 1979; Duensing 2000; Rojas-Ortega 2003). Laparoscopic cholecystectomy is currently preferred over open cholecystectomy for elective cholecystectomy (NIH 1992; Fullarton 1994; Livingston 2004; Keus 2006) and is advised only for symptomatic gallstones (NIH 1992).

Porcelain gallbladder (ie, calcified gallbladder) has been reported to be associated with a 7% risk of gallbladder cancer (Stephen 2001). Although the association between porcelain gallbladder and gallbladder cancer has been challenged (Towfigh 2001), prophylactic cholecystectomy is currently recommended for porcelain gallbladder (NIH 1992). Gallbladder polyps or suspected gallbladder polyps, more than 10 mm in size, have also been found to be associated with gallbladder cancer (Okamoto 1999; Lee 2004; Chattopadhyay 2005) and may be an indication for cholecystectomy. Cholecystectomy in the absence of symptoms is also controversial in diabetics, in immunosuppressed, and in children. Currently, there is no clear evidence to support prophylactic cholecystectomy in these groups, ie, in diabetics (Del Favero 1994), in immunosuppressed (NIH 1992; Jackson 2005), in children (NIH 1992), or in any other group.

Thus, surgery for silent gallstones represents a therapeutic dilemma (Gibney 1990; Bittner 2004; Gupta 2004), but should be considered for the following reasons:
(1) Complications associated with gallstones.
(a) Pancreatitis. Gallstone is one of the important aetiological factors for acute pancreatitis responsible for nearly 45% of acute severe pancreatitis (Gloor 2001). Acute pancreatitis has a mortality rate of 10% (Corfield 1985; Mann 1994). At present there are no clear predictive factors of the risk of pancreatitis from the size of the gallstone or motility of gallbladder (Venneman 2005).
(b) Cholecystitis (NIH 1992).
(c) Obstructive jaundice. Treatment for common bile duct stones may involve open common bile duct exploration (Sarli 2003) or laparoscopic exploration (Hyser 1999; Rojas-Ortega 2003; Waage 2003; Ebner 2004) or endoscopic retrograde cholangiopancreatography (ERCP) (Cuschieri 1999; Turcu 2000; Huttl 2002; Ludwig 2002; Enochsson 2004), all of which carry morbidity (Wills 2002; Christensen 2004).
(d) Gallbladder cancer. Studies have shown a high degree of correlation between gallstones and gallbladder cancer (Black 1977; Amir 1990; Launoy 1993; Okamoto 1999). Some studies have shown that the relative risk for gallbladder cancer is about 4.4 in the presence of gallstones (Lowenfels 1985). Other studies have questioned prophylactic cholecystectomy on the grounds that only 11% of the patients with gallbladder cancer had gallstones for more than one year (Broden 1980).
(2) Studies have shown that laparoscopic cholecystectomy, performed in persons with asymptomatic gallstones, has significantly lower morbidity rates, conversion rates, and operating time as compared to that performed in patients with symptomatic gallstones (Yano 2003).
(3) Studies have shown that the morbidity of laparoscopic cholecystectomy increases with age (Bittner 2004).

However, cholecystectomy is not without risks (Keus 2006). The risks include:
(1) Mortality due to the various complications.
(2) Injury to vessels or bowel (Fletcher 1999) during port insertion for laparoscopic cholecystectomy.
(3) Bile duct injury. The reported incidence of bile duct injury is between 0.3% (Richardson 1996; Krahenbuhl 2001) and 1% (Buanes 1996). Major bile duct injuries can even cause death due to uncontrolled sepsis (Sicklick 2005). Corrective surgery for bile duct injury carries its own risks including mortality (Schmidt 2005; Sicklick 2005), bile leak (Schmidt 2005; Sicklick 2005), cholangitis (Johnson 2000; Schmidt 2005; Sicklick 2005), biliary stricture (Johnson 2000; Huang 2003; Schmidt 2005), and biliary cirrhosis (Schmidt 2005).
(4) Bile leak requiring ERCP (Johansson 2003; Kimura 2005). ERCP has its own risks of mortality, pancreatitis, haemorrhage, and perforation (Christensen 2004).

The alternative treatments for gallstones are dissolution of stones by oral bile acids alone or in combination with other drugs (Tuncer 2003), contact dissolution using methyl-terbutyl ether (Hellstern 1998) or ethyl propionate (Zakko 1997), or shockwave lithotripsy with or without bile acids (Ertan 1992; Sauter 1997). However, these treatments leave the gallbladder behind and recurrence of gallstones is common (Avci 1993; Sackmann 1994; Pauletzki 1995; Hellstern 1998; Cesmeli 1999). Primary treatment failure is common (Petroni 1995), and prolonged treatment is needed for complete dissolution of stones (Tuncer 2003).

We have not been able to identify any systematic reviews or meta-analyses comparing cholecystectomy versus no cholecystectomy for patients with asymptomatic gallstones.

OBJECTIVES

To assess the benefits and harms of prophylactic cholecystectomy in patients with asymptomatic gallstones.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised clinical trials (irrespective of language, blinding, or publication status) were to be considered for this review.

Quasi-randomised studies (where the method of allocating participants to a treatment are not strictly random, eg, date of birth, hospital record number, alternation), cohort studies, and case-control studies were to be excluded from this review.

Types of participants

Patients who have asymptomatic gallstones. Patients with symptoms including cholecystitis, pancreatitis, obstructive jaundice, and biliary colic were excluded from the review.

Types of interventions

We were to include only trials comparing cholecystectomy (whether performed through an open access or laparoscopic access) versus no cholecystectomy.

The following types of trials were excluded.

1. Trials comparing cholecystectomy versus medical treatment.
2. Trials comparing medical treatment versus no treatment.
3. Trials comparing open cholecystectomy versus laparoscopic cholecystectomy.

Types of outcome measures

Primary outcomes

1. Mortality (at maximal follow-up).
2. Bile duct injury.
3. Acute severe pancreatitis.

Secondary outcomes

1. Cholecystitis.
2. Obstructive jaundice.
3. Bile leak requiring drainage:
   a. Surgical drainage,
   b. Image guided drain insertion,
   c. Image guided aspiration.
4. Bile leak requiring ERCP.
5. Other morbidity such as wound infection, intra-abdominal collections requiring drainage, infected intra-abdominal collections.
6. Number of hospital admissions (for complications or treatment of complications of gallstones).
7. Length of stay (for surgery, complications, or treatment of complications of gallstones).
8. Gallbladder cancer.
9. Number of workdays lost (because of surgery or because of symptoms).
10. Quality-of-life measures (however reported by authors).

Search methods for identification of studies

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE,* and *Science Citation Index Expanded* until May 2008 (Royle 2003). We have given the search strategies with the timespan for the searches in Appendix 1.

References of the identified studies were also searched for identifying studies of possible interest.

Data collection and analysis

Study selection and extraction of data

Both authors independently of each other identified the studies for possible inclusion. The excluded studies conducted on the relevant population with the reasons for the exclusion were to be listed in 'Excluded studies'. There were no differences in opinion.

Both authors had planned to independently extract the following data:

1. Year and language of publication.
2. Country.
3. Year of study.
4. Inclusion and exclusion criteria.
5. Sample size.
6. Population characteristics such as age and sex.
7. Open or laparoscopic cholecystectomy.
8. Peri-operative antibiotics.
9. Drain used or not.
10. Outcomes (mentioned above).
11. Methodological quality (described below).

Any unclear or missing information was to be sought by contacting the authors of the individual trials. We planned to contact the authors of the reports of the trials if there was any doubt whether the trials shared the same patients - completely or partially (by identifying common authors and centres) to clarify whether the report had been duplicated.

Assessment of methodological quality

We had planned to assess the methodological quality of the trials independently, without masking of the study names should we have found trials for inclusion. We had planned to follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2008). Due to the risk of overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), we had planned to look at the influence of methodological quality of the trials on the trial results by evaluating the reported randomisation and follow-up procedures in each trial. If information was not available in the published trial, we intended to contact the authors in order to assess the trials correctly. We had planned to assess generation of allocation sequence, allocation concealment, blinding, and follow-up.

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described. (The authors will be contacted and attempts will be made to find out the allocation method.)
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies are known as quasi-randomised and we planned to exclude them from the review.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.

- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. We planned to exclude such trials from the review.

Blinding

We did not plan to assess double blinding as it is not possible to blind the patients. The health-care providers (the surgeons) would have to be informed of any complications that occurred during the waiting period in order to assess the appropriate treatment required for the patient. However, it is possible to blind the observers for outcomes such as quality of life. We planned to consider blinding to be adequate if observer blinding was performed.

- Adequate, if the outcome assessors were blinded and the method of blinding was described.
- Unclear, if the outcome assessors were blinded and the method of blinding was not described.
- Not performed, if the outcome assessors were not blinded.

Incomplete data outcomes

- Adequate, if there were no post-randomisation drop-outs or withdrawals or if the post-randomisation drop-outs were balanced in both groups or reasons for missing data unlikely to be related to true outcome.
- Unclear, if it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear.
- Inadequate, if the reasons for missing data are likely to be related to true outcomes, "as-treated" analysis was performed, potentially inappropriate application of simple imputation, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Adequate, if all the important outcomes were reported or if the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- Unclear, if there is insufficient information to assess whether the risk of selective outcome reporting is present.
- Inadequate, if not all the pre-specified outcomes were reported or if the primary outcomes were changed or if some of the important outcomes were incompletely reported.

Other biases

Baseline imbalance

- Adequate, if there was no baseline imbalance in important characteristics.
- Unclear, if the baseline characteristics were not reported.
- Inadequate, if there was an baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Early stopping

- Adequate, if sample size calculation was reported and the trial was not stopped or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was low.
- Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.
- Inadequate, the trial was stopped early due to an informal stopping rule or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.

Blocked randomisation in unblinded trials

- Adequate, if blocked randomisation was used or blinding was adequate or if the blocks were of variable size or if the blocks were distributed across multiple centres such that it is not possible to predict the block size in a single centre.
- Unclear, if the method of blocked randomisation was not described.
- Inadequate, if it was possible to predict future assignments of participants based on previous assignments such as when fixed size blocks were used in a centre when the blinding was inadequate.

Source of funding

- Adequate, if the trial was unfunded or was not funded by an instrument manufacturer.
- Unclear, if the source of funding was not clear.
- Inadequate, if the trial was funded by an instrument manufacturer.

Statistical methods

We planned to perform the meta-analyses according to the recommendations of The Cochrane Collaboration (Higgins 2008). We planned to use the software package RevMan 2008. For dichotomous variables, we planned to calculate the risk ratio with 95% confidence interval. We planned to use a random-effects model (DerSimonian 1986) and a fixed-effect model (Demets 1987). In case of discrepancy between the two models we would have reported both results; otherwise we planned to report only the results from the fixed-effect model.

We planned to perform subgroup analyses depending on the methodological quality of the trials in order to compare the intervention effect in trials with adequate methodological quality to that of trials with unclear or inadequate methodological quality. We planned to explore heterogeneity by chi-squared test with significance set at P value 0.10, and measure the quantity of heterogeneity by I^2 (Higgins 2002).

Whenever possible, we planned to performed the analysis on an intention-to-treat basis (Newell 1992). Otherwise, we planned to perform 'available case analysis'. We planned to perform a sensitivity analysis with and without empirical continuity correction factors as suggested by Sweeting et al in case we found 'zero-event' trials (Sweeting 2004).

Subgroup analysis

We planned to perform the following subgroup analyses:
- trials with high (adequate allocation concealment) compared to trials with low methodological quality (unclear allocation concealment).
- trials using blinded outcome assessment to trials with blinded outcome assessment.
- laparoscopic versus open cholecystectomy.

- trials that use routine antibiotic prophylaxis (for surgery) compared to those that do not use routine antibiotic prophylaxis.

Bias exploration

We planned to use a funnel plot to explore publication bias and other bias (Egger 1997; Macaskill 2001). Asymmetry in funnel plot of study size against treatment effect was to be used to identify this bias. We also planned to perform linear regression approach described by Egger to determine the funnel plot asymmetry (Egger 1997).

RESULTS

Description of studies

We identified a total of 667 references through electronic searches of *The Cochrane Hepato-Biliary Group Controlled Trials Register* and the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (n = 103), *MEDLINE* (n = 363), *EMBASE* (n = 160), and *Science Citation Index Expanded* (n = 41). We excluded 209 duplicates and the remaining 458 references after having read titles and abstracts.

Risk of bias in included studies

None of the studies identified through the search strategy qualified for inclusion in this review. We were also unable to identify any cohort studies or any case-control studies that could meaningfully try to answer the questions posed in this systematic review.

Effects of interventions

None of the studies identified through the search strategy qualified for this review.

DISCUSSION

None of the studies identified through the search strategy qualified for this review. We were also unable to identify non-randomised studies, which could give information to answer the posed question. Accordingly, we have been unable to identify evidence, which could guide us. Therefore, there seems to be an urgent need for studies on whether to perform cholecystectomy in patients with asymptomatic gallstones. Ethical considerations of exposing 100 patients to the risk of surgery to prevent gallstone-associated complications in 10 to 15 patients (ie, exposing 85 to 90 patients to the risks of surgery unnecessarily) has to be considered before designing randomised trials to compare cholecystectomy versus no cholecystectomy. Studies, in which prophylactic cholecystectomy was performed for asymptomatic gallstones based on patient's preference (as some patients may prefer to have their gallbladders removed when all the facts are told to them), might throw some light into this issue. Also, further evaluation of the studies in which cholecystectomy was performed routinely and those in which cholecystectomy was not performed for asymptomatic gallstones has to be performed. The follow-up of these studies should be of sufficient duration to demonstrate a reduction in the incidence of obstructive jaundice, gallstone-associated pancreatitis, and/or gallbladder cancer to justify the exposure of the patients with asymptomatic gallstones to the complications of surgery in the trial.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence in literature to either recommend or refuse surgery to patients with asymptomatic gallstones.

Implications for research

Observational studies, which measure outcomes such as obstructive jaundice, gallstone-associated pancreatitis, and/or gallbladder cancer for sufficient duration of follow-up is necessary. Such studies could help to determine the dimension and duration of follow-up of randomised clinical trials designed to evaluate whether cholecystectomy or no cholecystectomy is better for asymptomatic gallstones.

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APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	May 2008	(cholecystolithiasis OR cholelithiasis) AND operation*
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 2, 2008	#1 CHOLELITHIASIS explode all trees (MeSH) #2 (cholecystolithiasis or cholelithiasis) #3 (#1 or #2) #4 operation* #5 (#3 and #4)

(Continued)

MEDLINE	1950 to May 2008	("Cholelithiasis"[Mesh] OR cholecystolithiasis or cholelithiasis) AND operation* AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) AND humans [mh])
Embase	1974 to May 2008	1 CHOLELITHIASIS#.W..DE. OR cholecystolithiasis OR cholelithiasis 2 operation$ 3 1 AND 2 4 RANDOM$ OR FACTORIAL$ OR CROSSOVER$ OR CROSS ADJ OVER$ OR PLACEBO$ OR DOUBL$ ADJ BLIND$ OR SINGL$ ADJ BLIND$ OR ASSIGN$ OR ALLOCAT$ OR VOLUNTEER$ OR CROSSOVER-PROCEDURE#.MJ. OR DOUBLE-BLIND-PROCEDURE#.DE. OR SINGLE-BLIND-PROCEDURE#.DE. OR RANDOMIZED-CONTROLLED-TRIAL#.DE. 5 3 AND 4
Science Citation Index Expanded	1945 to May 2008	#1 TS=(cholecystolithiasis or cholelithiasis) #2 TS=(operation*) #3 #1 AND #2 #4 TS=(random* or placebo* or blind* or meta-analysis) #5 #3 AND #4

WHAT'S NEW

Date	Event	Description
9 September 2008	New search has been performed	New searches performed May 2008. Still no studies available. Components for bias assessment updated.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 1, 2007

Date	Event	Description
26 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

KS Gurusamy prepared the review and assessed the trials for inclusion. K Samraj is the co-author of the protocol and independently assessed the trials for inclusion and contributed to the discussion.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- none, Not specified.

External sources

- none, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol and the updated review (Issue 1 2009)

We updated the components for assessing the risk of bias of the trials in line with the recommendations of the updated Cochrane Handbook in 2008. We included two additional secondary outcomes:
- other morbidity such as wound infection, intra-abdominal collections requiring drainage, infected intra-abdominal collections and
- number of workdays lost (because of surgery or because of symptoms).

INDEX TERMS

Medical Subject Headings (MeSH)

*Cholecystectomy; Gallstones [*surgery]

MeSH check words

Humans