Meta-analysis of cholecystectomy in symptomatic patients with positive hepatobiliary iminodiacetic acid scan results without gallstones

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CRD summary
The review found that among patients without gallstones, but with right upper quadrant pain and a positive hepatobiliary iminodiacetic acid scan, cholecystectomy was more likely to relieve symptoms than medical treatment. In view of probable selection bias, poor reporting of study characteristics, clinical differences between studies and high levels of statistical heterogeneity, the conclusions may not be reliable.

Authors' objectives
To determine whether cholecystectomy is indicated for treatment of right upper quadrant pain and a positive hepatobiliary iminodiacetic acid (HIDA) scan in patients without gallstones.

Searching
PubMed (1989 to March 2007), EMBASE and The Cochrane Library were searched without language restrictions. Search terms were reported. Proceedings of major gastro-intestinal meetings and reference lists of relevant studies and reviews were handsearched.

Study selection
Comparative studies of open or laparoscopic surgery versus medical treatment for symptomatic patients without gallstones or structural biliary abnormalities (as confirmed by imaging) were eligible for inclusion. Patients were required to have a gallbladder ejection fraction of 50% or less on cholecystokinin HIDA scan. Symptoms could include right upper quadrant pain, epigastric and/or postprandial pain, nausea, vomiting and other symptoms. Studies were required to report symptom resolution (complete, partial, none or worse). Data could be collected by face-to-face or phone interview and/or by questionnaire. Studies in which participants on medical treatment subsequently underwent surgery were excluded.

Most of the included studies were conducted in USA. Participants were predominantly female in the only two studies that reported this information. In most cases a threshold of 35% was used to define abnormal gallbladder ejection fraction. Dose and infusion rate of cholecystokinin varied across studies. Outcome assessment was mostly by telephone interview, sometimes combined with clinic interview. Duration of follow-up ranged from one to 144 months.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Study quality was evaluated with the Newcastle Ottawa Scale for non-randomised studies (up to nine stars for quality).

The authors did not state how many reviewers assessed study validity.

Data extraction
Data were extracted on treatment response, classified as complete, partial or no response/symptoms worse. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). The Haldane correction was applied, adding 0.5 to event rates if no events occurred in one group.

Three reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Studies were combined using the Mantel-Haenszel random-effects model to calculate combined odds ratios and 95%
CIs. Statistical heterogeneity was assessed using the $I^2$ test. Publication bias was assessed with funnel plots and Begg and Egger tests. Sensitivity analyses were conducted by outcome (level of symptom relief), study quality (more than six stars), study size (excluding the largest study), definition of ejection fraction (threshold 35% versus 50%), cholecystokinin dose and duration and length of follow-up.

**Results of the review**

Ten studies were included ($n=615$, range 11 to 181) with 462 participants in the surgical groups and 153 in the medical groups. The studies were apparently of observational design. Six studies scored more than six stars for quality. None of the studies used blinding.

Compared to medical therapy, surgery was associated with a significantly greater likelihood of any symptom relief (OR 16.26, 95% CI 3.82 to 69.19; 10 studies, $I^2=72.3\%$).

In sensitivity analyses, surgery was significantly associated with greater likelihood of complete symptom relief (nine studies, $n=434$), but there was no significant difference between the groups for partial symptom relief (nine studies, $n=604$). All other sensitivity analyses showed significant benefit from surgery for complete and/or any symptom relief. There was significant statistical heterogeneity for all sensitivity analyses: $I^2$ ranged from 57.4% to 92.5%. Funnel tests were suggestive of publication bias, but this was not evident in statistical testing.

**Authors’ conclusions**

Among patients without gallstones and with right upper quadrant pain and a positive HIDA scan, cholecystectomy was more likely to relieve symptoms than medical treatment.

**CRD commentary**

The main objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without restriction by language or publication status. It was unclear whether one of the aims of the review was to determine the predictive power of a positive HIDA scan: if so, the review design was unsuitable to meet this objective. Steps were taken to minimise risks of reviewer bias and error by having multiple reviewers independently extract the data; methods used for study selection and validity assessment were not described. The information provided about the design of the included studies was scanty and inconsistent. No details were reported about components of study quality or about any of the medical interventions used. Despite extensive sensitivity analyses, there was very marked heterogeneity for all outcomes, which remained largely unexplained. Most of the studies were small and there was marked inequality between the size of the comparison groups. It appeared likely that comparison groups had differing prognostic factors at baseline, as suggested by the review authors. This suggests that there was selection bias in the primary studies, whereby participant characteristics influenced which intervention they would receive. There was some suggestion of publication bias; this was not confirmed by statistical testing. Confidence intervals were very wide for some findings.

In view of probable selection bias in the primary studies, poor reporting of study characteristics, clinical differences between the studies and high levels of statistical heterogeneity in all analyses, the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that in symptomatic patients without gallstones, a HIDA scan with a low ejection fraction was a legitimate indicator for cholecystectomy and predicted favourable postoperative outcomes. However, the review was not designed to assess the prognostic significance of the HIDA scan as it did not include studies of patients with normal HIDA scans.

**Research:** The authors did not state any implications for research.

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