Laparoscopic cholecystectomy versus conservative management for adults with uncomplicated symptomatic gallstones: the C-GALL RCT

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Scientific summary

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Scientific summary

Background

Gallstone disease is one of the most common gastrointestinal disorders in industrialised societies. The prevalence of gallstones in the adult population is estimated to be approximately 10–15%, and around 80% remain asymptomatic. Prevalence increases with age and obesity and is higher in women than in men. At present, cholecystectomy is the default option for people with symptomatic gallstone disease. However, some people, after an initial episode of biliary pain or cholecystitis, do not experience persistent symptoms or complications. There is, therefore, an indication that uncomplicated symptomatic gallstone disease may not always require removal of the gallbladder and could be treated conservatively.

Objectives

To assess the clinical and cost-effectiveness of observation/conservative management compared with laparoscopic cholecystectomy for preventing recurrent symptoms and complications in adults presenting with uncomplicated symptomatic gallstones in secondary care.

Methods

Design

Parallel-group, multicentre patient randomised superiority pragmatic trial with up to 24 months follow-up and embedded qualitative research. Within-trial cost–utility and 10-year Markov model analyses. Development of a core outcome set for uncomplicated symptomatic gallstone disease.

Setting

Secondary care elective settings.

Participants

Adults with symptomatic uncomplicated gallstone disease referred to a secondary care setting.

Exclusion criteria

Unable to consent, medically unfit for surgery, current pregnancy, previous open major upper abdominal surgery, gallstones in the common bile duct or evidence of previous choledocholithiasis, history of acute pancreatitis, evidence of obstructive jaundice, evidence of empyema of the gallbladder with sepsis, suspicion of gallbladder cancer, perforated gallbladder (recent or old perforation) and haemolytic disease.

Primary outcome

Quality of life (QoL) measured by area under the curve (AUC) over 18 months using the Short Form-36 items (SF-36) bodily pain domain.

Secondary outcomes

Otago gallstones Condition-Specific Questionnaire (CSQ).
SF-36 domains (excluding bodily pain).
AUC over 24 months for SF-36 bodily pain.
Persistent symptoms.
Complications.
Need for further treatment.

Sample size

The sample size calculation was based on the primary outcome, AUC up to 18 months using SF-36 bodily pain. A total of 430 participants was needed to detect a 0.33 standard deviation (SD) difference with 90% with alpha at 5% and allowing 10% of participants with complete missing outcome data.

Randomisation

Participants were randomised at a 1 : 1 allocation ratio, using the randomisation application at the trial office at the Centre for Healthcare Randomised Trials (CHaRT). The minimisation variables were recruitment site, gender (male/female) and age (< 35; 35–64; ≥ 65 years) as minimisation covariates to allocate treatment. A random element (20% chance) was incorporated into the minimisation algorithm.

Primary economic outcomes

Incremental cost per quality-adjusted life-year (QALY). QALYs were estimated using participants' responses to the SF-36 questionnaire and were assigned a utility score based on the SF-6D UK tariff.

Interventions: health technology assessed

1. Laparoscopic cholecystectomy.
2. Observation/conservative management.

Results

Clinical effectiveness

Participants were recruited to the C-GALL trial between August 2016 and November 2019. In total, 434 participants were randomised from 20 centres within the UK. There were 2667 patients identified to be potentially eligible for inclusion into the trial, of which 1298 were excluded. Of the 1369 eligible patients, 933 were not randomised, with 910/933 (97.5%) having a preference. The main preference reasons were participants preferred cholecystectomy (538/910, 59.1%), observation/conservative management (167/910, 18.4%) and did not want to be randomised (91/910, 10.0%). By 18 months, 54 (24.9%) in the observation/conservative management group and 146 (67.3%) in the laparoscopic cholecystectomy group received surgery. By 24 months, 64 (29.5%) in the observation/conservative management group and 153 (70.5%) in the laparoscopic cholecystectomy group received surgery with a median time to surgery of 9.0 months [interquartile range (IQR) 5.6–15.0] and 4.7 months (IQR 2.6–7.9), respectively.

At 18 months, the mean SF-36 norm-based bodily pain score was 49.4 (SD 11.7, *n* = 135) in the observation/conservative management group and 50.4 (SD 11.6, *n* = 138) in the laparoscopic cholecystectomy group. For the primary analysis, the mean AUC over 18 months was 46.8 for both groups with no difference with 203 in the observation/conservative management group and 205 in laparoscopic cholecystectomy group providing data: mean difference (MD) −0.0, 95% confidence interval (CI) (−1.7 to 1.7); *p*-value 0.996.

The mean CSQ at 18 months was 21.3 (SD 21.0, *n* = 113) for the observation/conservative management group and 15.8 (SD 19.7, *n* = 101) for the laparoscopic cholecystectomy group and showed evidence of a difference in favour of laparoscopic cholecystectomy: MD 6.6, 95% CI (1.9 to 11.3); *p*-value 0.006. At 24 months, there was evidence of a difference in favour of laparoscopic cholecystectomy (*n* = 205) compared with observation/conservative management group (*n* = 203): MD 9.0, 95% CI (4.1 to 14.0), *p*-value < 0.001. There was a similar pattern for the persistent symptoms score.

At 18 months, 32 (10.1%) participants in the observation/conservative management group had had a complication compared with 44 (25.3%) participants in the laparoscopic cholecystectomy group, with no

evidence of a difference between groups: RR 0.72, 95% CI (0.46 to 1.14); *p*-value 0.17. At 24 months, there were an additional two complications in the laparoscopic cholecystectomy group.

Prespecified sensitivity analyses demonstrated clearly that compliance with treatment allocation, missing data and the potential impact of COVID-19 did not change the findings.

Cost-effectiveness

Cost analysis shows that observation/conservative management group was less costly than the laparoscopic cholecystectomy (MD −£1033). The trial did not demonstrate a significant difference in QALYs between the groups – a mean QALY difference of −0.019 favoured cholecystectomy. The base-case incremental cost-effectiveness ratio (ICER) was found to be high (£55,235), meaning significant potential savings to the NHS with limited QALY loss by following an observation/conservative management approach in the short term. Longer-term modelling suggested that following an observation/conservative management approach might be cost-effective, but there was greater uncertainty due to limited information on subsequent surgeries in the randomised groups, and differences in quality of life (QoL) beyond 24 months could reverse this finding. Sensitivity analysis incorporating longer-term QoL scores reduced the potential saving to just £14,700 per QALY lost. The current decision uncertainty could be reduced with a long-term follow-up of the C-GALL trial participants.

Process evaluation

The embedded process evaluation in C-GALL explored ways to improve recruitment and retention across the trial. A total of 16 sites provided 180 audio recordings of consultations for analysis. Analysis of the transcripts identified four core challenge areas for recruiters: (1) providing a balanced presentation about both treatments; (2) discussing and exploring preferences; (3) discussing uncertainty; and (4) discussing participants who did not receive their treatment allocation (crossovers in treatments). A subset of 38 audio recordings of consultations from four sites were included in the analysis of discussion of retention. Thirty (79%) of these consultations did not include any discussion of trial retention. Interviews with participants (n = 9) to explore challenges in returning postal questionnaires identified six themes influencing retention: unclear expectations of trial participation; personal attributes for questionnaire completion; significance of questionnaire non-return; commitment to returning questionnaires given other priorities; individual preferences for presentation mode and timing of the questionnaires and, internal and external strategies to encourage questionnaire return. The innovative adoption of a behavioural science approach to the process evaluation led to structured changes in written and verbal information across the trial including e-mail feedback, amendments to trial information leaflet and updates to cover letters and newsletters.

Core outcome set

The final core outcome set (COS) for symptomatic uncomplicated gallstone disease included 11 critically important outcomes from both patients and healthcare professionals. These were: QoL; overall health state; overall satisfaction; overall pain; common bile duct injury; biliary leak; haemorrhage; need for endoscopic retrograde cholangiopancreatography; intra-abdominal collections; admission/re-admission for problems; and reoperation.

Comparison with similar randomised trials

The clinical outcomes were similar to those seen in previous randomised trials. The economic outcomes, as they relate to the UK NHS, have not been evaluated in previous randomised trials.

Strengths of the study

C-GALL's strengths included the pragmatic randomised controlled trial (RCT) design and methodological rigour. The benefit of the sample size is reflected in the precision with which outcomes were estimated. This multicentre trial also gives confidence in the generalisability of findings to the NHS. Comparison with routine data suggests that the results were representative of the UK population with gallstones.

This trial was pragmatic where patients in the UK may not always receive the treatment they are offered and waiting lists for surgical treatment exist. We carefully tracked treatment after randomisation and monitored compliance. A major strength included our sensitivity analyses, including compliance analysis, imputation for missing data and potential impact of coronavirus disease 2019 (COVID-19). These analyses did not change our findings.

The cost-effectiveness analysis had several strengths. Firstly, the RCT design allowed the collection of data on resource use and QoL collected prospectively for comparable groups. Secondly, in cost analysis, critical model data was supported by RCT data (e.g. survival analysis; QoL data for the reduction in QoL weight before and after surgery).

We incorporated an embedded process evaluation with qualitative interviews to better understand and reduce recruitment and retention challenges. The process evaluation gave some generalisable findings and recommendations for good practice for ongoing and future trials including how to improve the informed consent and follow-up processes.

A key strength of the COS was the extensive outcome mapping exercise on which the COS was built. The development of a core outcome set for uncomplicated symptomatic gallstone disease will help to ensure that important outcomes to patients and the NHS are collected in the future.

Limitations of the study

An unexpected difficulty was the longer-than-expected time on the waiting list for surgery for those patients who were allocated to cholecystectomy. When designing the trial, it was anticipated that this wait would be, on average, 6 months. Therefore an 18-month follow-up was chosen as the primary outcome follow-up time to reflect a time equivalent to 12 months after surgery. However, during the study, we observed that patients often experienced longer times to surgery, initially due to limited existing NHS resources that resulted in longer waiting lists. To address this, we added a 24-month follow-up time point. Our sensitivity analyses on compliance with the treatment suggested that the waiting list was unlikely to be biasing the study findings. The existence of the waiting list may limit the generalisability to some other countries' jurisdictions. A further limitation was the non-blinding of participants and treating surgeons to allocation.

Implications for health care

Current clinical guidelines recommend laparoscopic cholecystectomy for biliary pain or acute cholecystitis and radiological evidence of gallstones. Hence, surgical management remains the default option for people with symptomatic gallstone disease, one of the most common elective surgical procedures performed in the NHS. In the UK, many people with uncomplicated symptomatic gallstone disease are put on a waiting list and operated on electively after several months. The C-GALL trial demonstrates that in adults presenting with uncomplicated symptomatic gallstones, in a secondary care setting, observation/conservative management may be more effective and cost-effective than laparoscopic cholecystectomy in the short term. The crossover between groups suggests that it remains

key to identify patients that will and will not require surgery, and as healthcare workers often underestimate surgical risks, discussion about conservative management should be part of the clinical discussion.

Implications for research

Costs and benefits will continue to be incurred in both groups beyond 24 months, so future research should focus on (1) long-term follow-up data to establish lifetime cost-effectiveness and (2) identification of the cohort of patients that should be offered surgery.

Conclusion

Overall, our results suggest that in the short term (up to 24 months) observation/conservative management may be a cost-effective use of NHS resources in selected patients, but subsequent surgeries in the randomised groups and differences in QoL beyond 24 months could reverse this finding, and longer-term follow-up is needed to verify the safety and cost-effectiveness of this approach.

Trial registration

This trial is registered as ISRCTN55215960.

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