

Clinical effectiveness and cost-effectiveness of cholecystectomy compared with observation/conservative management for preventing recurrent symptoms and complications in adults presenting with uncomplicated symptomatic gallstones or cholecystitis: a systematic review and economic evaluation

Miriam Brazzelli,^{1*} Moira Cruickshank,¹
Mary Kilonzo,² Irfan Ahmed,³ Fiona Stewart,¹
Paul McNamee,² Andrew Elders,¹ Cynthia Fraser,¹
Alison Avenell¹ and Craig Ramsay¹

¹Health Services Research Unit, University of Aberdeen, Aberdeen, UK

²Health Economics Research Unit, University of Aberdeen, Aberdeen, UK

³NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK

*Corresponding author

Declared competing interests of authors: none

Published August 2014

DOI: 10.3310/hta18550

Scientific summary

Cholecystectomy compared with observation/conservative management

Health Technology Assessment 2014; Vol. 18: No. 55

DOI: 10.3310/hta18550

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Gallstone disease, cholelithiasis, is the most common and costly gastrointestinal disorder in industrialised countries. Prevalence increases with age and obesity and is higher in women than in men.

In about 20% of people, the condition is symptomatic and can cause severe pain and complications which require medical attention and/or emergency surgery. Cholecystectomy, the surgical removal of the gallbladder, is the treatment of choice for people who present with biliary pain or acute cholecystitis and evidence of gallstones. Nowadays cholecystectomy is performed preferably by means of laparoscopic procedures. However, some people, after an initial episode of biliary pain or cholecystitis, do not experience persistent symptoms or complications. Natural history and population-based studies have shown that around half of symptomatic people do not experience further episodes of pain. There is, therefore, an indication that uncomplicated symptomatic gallstone disease (biliary pain or cholecystitis) does not always require removal of the gallbladder and could be treated conservatively. This assessment was designed to help inform decisions regarding the use in clinical practice of conservative management and cholecystectomy for adults with uncomplicated symptoms or cholecystitis. In particular, this assessment aimed to:

- describe the clinical care pathways of uncomplicated symptomatic gallstone disease (biliary pain or cholecystitis) in a UK NHS context
- determine the clinical effectiveness and safety of conservative management compared with cholecystectomy
- perform a systematic review of the evidence available on the cost-effectiveness of cholecystectomy compared with conservative management
- determine which treatment option is most likely to be cost-effective for implementation in the UK NHS
- identify and prioritise future research needs.

Methods

We searched major bibliographic electronic databases from 1980 to September 2012 including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Science Citation Index, Bioscience Information Service and the Cochrane Central Register of Controlled Trials. Reports of relevant evidence syntheses were also sought from the Cochrane Database of Systematic Reviews and the Database of Abstracts of Review of Effects. Evidence was considered from randomised controlled trials (RCTs) or non-randomised comparative studies in which people received either cholecystectomy or observation/conservative management. The population was adults with first episode of symptomatic gallstone disease (biliary pain or cholecystitis) being considered for surgical treatment in a secondary care setting. The intervention considered was cholecystectomy (open or laparoscopic). The comparator was observation and/or conservative management. One reviewer screened the titles and abstracts of all reports identified by the search strategies and two reviewers independently screened all full-text papers retrieved for this assessment. Two reviewers independently extracted data and assessed the risk of bias of included studies. Standard meta-analysis techniques were used to combine results from included studies.

A de novo Markov model was developed to assess the cost-effectiveness of observation/conservative management compared with cholecystectomy. Parameter estimates were derived from the systematic review of clinical effectiveness, current literature, the expert advisory group for this assessment and other UK sources. The outputs of the model were costs and quality-adjusted life-years (QALYs) for each

treatment strategy, incremental costs and QALYs and incremental cost per QALY for a 5-year time horizon. Costs were considered from a health services perspective. Costs were discounted at 3.5% per year in accordance with the current National Institute for Health and Care Excellence guidelines. Probabilistic and deterministic sensitivity analyses were applied to the model in order to assess the robustness of the results to realistic variations in the model parameters.

Results

Clinical effectiveness

The literature searches identified 6779 potentially relevant citations, of which 73 reports were selected for full-text eligibility screening. Two RCTs published in six reports and involving 201 participants were subsequently deemed suitable for inclusion. Both trials, conducted in Norway, were considered to be at low risk of bias for all assessed quality domains. The results demonstrated that 88% of people randomised to surgery and 45% of people randomised to observation eventually underwent cholecystectomy during the 14-year follow-up period. Participants randomised to observation were significantly more likely to experience gallstone-related complications [risk ratio = 6.69; 95% confidence interval (CI) 1.57 to 28.51; $p = 0.01$], in particular acute cholecystitis (risk ratio = 9.55; 95% CI 1.25 to 73.27; $p = 0.03$), and less likely to undergo surgery (risk ratio = 0.50; 95% CI 0.34 to 0.73; $p = 0.0004$), experience surgery-related complications (risk ratio = 0.36; 95% CI 0.16 to 0.81; $p = 0.01$) or, more specifically, minor surgery-related complications (risk ratio = 0.11; 95% CI 0.02 to 0.56; $p = 0.008$) than those participants randomised to surgery. Among participants with an initial diagnosis of uncomplicated symptomatic gallstones (biliary pain only) rather than cholecystitis, those randomised to observation were significantly more likely to experience pain attacks after randomisation ($\chi^2 = 9.10$; $p = 0.0026$) and to be admitted to hospital for gallstone-related pain ($\chi^2 = 7.79$; $p = 0.0053$) than those randomised to surgery. Mortality risk was greater (but not significantly greater) among participants randomised to surgery. Fifty-five per cent of people randomised to observation did not require an operation during the 14-year follow-up period and 12% of people randomised to cholecystectomy did not undergo the scheduled operation.

Cost-effectiveness

The results of the economic evaluation showed that, on average, the surgery strategy cost £1236 more than the conservative management strategy but was, on average, more effective, and generated 0.094 additional QALYs. The incremental cost per QALY was £13,205. The result of the incremental cost-effectiveness analysis indicated that the conservative management strategy had a 51% chance of being considered cost-effective when society's willingness to pay for a QALY was £20,000 and a 46% chance when willingness to pay was £30,000. The probability of cost-effectiveness was not sensitive to changes in the threshold, when the threshold increased to £30,000, the surgery strategy had a 51% chance of being considered cost-effective. The results were sensitive to the probability of people in conservative management undergoing cholecystectomy. An increase in the number of people requiring surgery while treated conservatively corresponded to a reduction in the cost-effectiveness of the conservative strategy. There was uncertainty around the estimate derived from the meta-analysis of clinical effectiveness. On average, the cost of the conservative management strategy was reduced to £694 when the probability of undergoing surgery was reduced to 25%, leading to an incremental cost-effectiveness ratio (ICER) of £33,542 per QALY for the surgical strategy. In contrast, the cost of the conservative management strategy increased to £1757, leading to a reduced ICER of £4291 when the probability of surgery among people initially managed conservatively was increased to 75%.

Strengths and limitations

The methods used to conduct this assessment were detailed and thorough. The main limitation of this assessment was the limited data currently available on the clinical effectiveness and safety of observation/conservative management compared with cholecystectomy for the treatment of uncomplicated symptomatic gallstone disease (biliary pain or cholecystitis) in the UK. The paucity of both utility and clinical effectiveness data added uncertainty to the economic evaluation.

Conclusions

The results of this assessment showed that approximately half of the people in the observation group were eventually operated on. Participants who underwent cholecystectomy experienced more surgery-related complications and showed a slight, non-significant, increase in the rate of all-cause mortality than those who were treated conservatively. In contrast, participants allocated to observation had more episodes of cholecystitis, but few other gallstone-related complications (e.g. common bile duct stones, acute pancreatitis). Approximately half of the people in the observation group did not require surgery in the long term, indicating that there is probably a subgroup of people with uncomplicated symptomatic gallstones who could benefit from conservative management.

Cholecystectomy is more costly to the NHS because of the use of resources associated with surgery and the costs related to the treatment of post-surgery complications. Our modelling shows that conservative management is, on average, less costly but also less clinically effective for the treatment of symptomatic gallstones. A policy of surgery for all, rather than a policy of conservative management followed by surgery among people whose symptoms persist, is likely to be more effective even though more costly. The difference between the two policies, however, is small. Uncertainty in the economic model was mostly driven by the pre- and post-surgery utility values, as well as by the future probability of receiving surgery following a strategy of conservative management.

Recommendations for future research

- A large, well-designed clinical trial needs to be undertaken to compare the effects and safety of observation/conservative management with cholecystectomy in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis to secondary care. This trial would contribute to identify factors which may allow the clinicians to single out people who are more likely to benefit from surgery from those at low risk of subsequent events and complications. Ideally, such a trial would include relevant outcome measures, such as post-cholecystectomy symptoms and quality-of-life measurements, and a full economic evaluation.
- Further research to evaluate the natural history of symptomatic gallstone disease (including uncomplicated cases).
- Research to elicit factors that may predict the evolution of symptoms in people with symptomatic gallstone disease.
- Research on people's personal preferences in terms of treatment options and outcomes.
- Research to identify resource use for people undergoing cholecystectomy (pre-operative assessment, surgical admissions and post-operative management) and for those receiving conservative management, in order to develop more robust cost estimates for the UK.

Study registration

This study is registered as PROSPERO CRD42012002817

Funding

The National Institute for Health Research Health Technology Assessment programme.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: <http://www.nets.nihr.ac.uk/programmes/hta>

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/16/01. The contractual start date was in August 2012. The draft report began editorial review in May 2013 and was accepted for publication in October 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen's Printer and Controller of HMSO 2014. This work was produced by Brazzelli *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson Director of NETSCC, HTA, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Professor Elaine McColl Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

Professor Jane Norman Professor of Maternal and Fetal Health, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, University College London, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk