This is the authors' final version, post peer-review, of an article published in *Surg Endosc* 2014;DOI 10.1007/s00464-014-3712-6. **The definitive version is available from** **www.springer.com**

Systematic review of the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for uncomplicated symptomatic gallstones or cholecystitis

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Source of funding: This review was commissioned by the UK NIHR HTA Programme (project number 12/16).

Abstract

Background

Gallstone disease is a common gastrointestinal disorder in industrialised countries. Although symptoms can be severe, some people can be symptom free for many years after the original attack. Surgery is the current treatment of choice but evidence suggests that observation is also feasible and safe. We reviewed the evidence on cholecystectomy versus observation for uncomplicated symptomatic gallstones and conducted a cost effectiveness analysis.

Methods

We searched six electronic databases (last search April 2014). We included randomised controlled trials (RCTs) or non-randomised comparative studies where adults received either cholecystectomy or observation/conservative management for the first episode of symptomatic gallstone disease (biliary pain or cholecystitis) being considered for surgery in secondary care. Meta-analysis was used to combine results. A *de novo* Markov model was developed to assess the cost-effectiveness of the interventions.

Results

Two RCTs (201 participants) were included. Eighty-eight percent of people randomised to surgery and 45% of people randomised to observation underwent cholecystectomy during the 14-year follow-up period. Participants randomised to observation were significantly more likely to experience gallstone-related complications (RR=6.69, 95% CI=1.57 to 28.51, p=0.01), in particular acute cholecystitis (RR=9.55, 95% CI=1.25 to 73.27, p=0.03), and less likely to undergo surgery (RR=0.50, 95% CI=0.34 to 0.73, p=0.0004) or experience surgery-related complications (RR=0.36, 95% CI=0.16 to 0.81, p=0.01) than those randomised to surgery. Fifty-five percent of people randomised to observation did not require surgery and 12% of people randomised to cholecystectomy did not undergo surgery. On average, surgery cost £1,236 more per patient than conservative management, but was more effective.

Conclusions

Cholecystectomy is the preferred treatment for symptomatic gallstones. However, approximately half the observation group did not require surgery or suffer complications indicating that it may be a valid alternative to surgery. A multicentre trial is needed to establish the effects, safety, and cost-effectiveness of observation/conservative management relative to cholecystectomy.

Keywords

Gallstones, cholecystectomy, observation, conservative management, systematic review, cost-effectiveness.

Introduction

Around 10 to 15% of adults in industrialised countries have gallstones [1-4], one of the most common and costly gastrointestinal disorders in these countries [1,5-9].

Approximately 20% of people with gallstones experience pain and/or clinical complications requiring medical attention and/or emergency surgery [1,5,6,10]. The remaining 80% of people with gallstones are asymptomatic [11,12], can be symptom free for many years and do not require treatment [11,12]. The treatment of choice for symptomatic gallstones is surgery (cholecystectomy), usually by means of laparoscopic procedures.

Findings of natural history studies suggest, however, that recurrent pain attacks subside in up to half of people [13] and surgery is not always necessary for people with gallstones [14,15]. In addition, there is evidence that it is feasible to conduct randomised controlled trials (RCTs) comparing the outcomes and safety of cholecystectomy and observation/conservative treatment in people with biliary colic/pain or acute cholecystitis [16]. Nevertheless, surgery remains the treatment of choice for symptomatic gallstones [17] and evidence of the relative clinical effectiveness of surgery and conservative management has yet to be synthesized.

A further consideration is the relative cost effectiveness of these treatment options. Costs, from the perspective of the health care system, include pre-operative hospital visits, hospital stays, operating theatre time and surgical instruments as well as the longer term resource impact on health care services associated with management or recurrence episodes of pain.

Therefore, the aim of this review was to systematically evaluate the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for preventing recurrent symptoms and complications in adults presenting initially with uncomplicated symptomatic gallstones for whom surgery is considered a treatment option.

Methods

Clinical effectiveness

A systematic review was conducted following the general principles of the Centre for Reviews and Dissemination guidance for undertaking reviews in health care and reported in accordance with the PRISMA statement [18,19].

Literature search

Comprehensive literature searches of the following electronic databases were conducted: MEDLINE, MEDLINE-in-process, Embase, Science Citation Index, BIOSIS and the Cochrane Central Register of Controlled Trials. Relevant sources were also searched for evidence syntheses, ongoing studies and conference proceedings. Reference lists of included studies were checked for potentially relevant reports. The date of the last searches was April 2014. A sample search strategy is presented in Appendix 1.

Study selection and data extraction

Randomised controlled trials and non-randomised comparative studies were included. The population was adults with symptomatic but 'uncomplicated' gallstone disease (biliary pain or acute cholecystitis) being considered for cholecystectomy in a secondary care setting for the first time. People presenting with acute severe cholecystitis, cholangitis or pancreatitis were not considered suitable for inclusion as usually they require urgent treatments. The intervention was laparoscopic or open cholecystectomy. The comparator interventions were observation (watchful waiting) and/or conservative treatment. The outcomes considered were disease-related morbidity i.e. recurrence of symptoms; complications (e.g. pancreatitis); number of visits to primary care settings or hospital emergency departments; analgesic requirements; need for surgical, endoscopic or radiological intervention; need for further medical intervention; mortality; surgery-related morbidity (bile duct injury; infection/bleeding; reoperation rate; diarrhoea; recurrent pain; mortality); patient-driven outcomes (i.e. generic and disease-specific quality of life); cost of initial and any subsequent treatments.

One reviewer screened all titles and abstracts identified by the search strategy. Two reviewers independently assessed all potentially relevant full text articles. Two reviewers independently extracted data from included studies. Risk of bias of included studies was assessed independently by two reviewers using the Cochrane Collaboration's risk of bias tool [20]. Domains assessed were sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. At all stages, disagreement between reviewers was resolved by consensus.

Quantitative synthesis

Meta-analyses (using Review Manager 5.2 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) were conducted where the same outcome was reported by more than one included study. The Mantel-Haenszel method was used to estimate risk ratios pooled across studies,

with corresponding 95% confidence intervals. Heterogeneity between studies was assessed by visual inspection of forest plots and from Mantel-Haenszel chi-squared and I−squared tests.

Cost effectiveness

A *de novo* Markov model was developed to assess the relative cost-effectiveness of cholecystectomy and observation/conservative management for this population. The structure of the model was informed by the findings of the trials included in the systematic review of clinical effectiveness, current literature, and expert advice from health care professionals within the research team. The perspective adopted for the analysis was that of the UK NHS and Personal Social Services. 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 the health services perspective and were discounted at 3.5% per year in accordance with the current NICE guidelines. The key assumptions of the economic modelling exercise were a 5-year time horizon, a one-year cycle length, and a 51-year old female as the base case. These assumptions were justified by the fact that the identified evidence suggested that very few people had cholecystectomy after 5 years from onset of symptoms in a hospital setting and that more women than men had cholecystectomy with an average age of 51 years. 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. Full details of the model's development and structure are available from the authors on request.

Results

Clinical effectiveness

Figure 1 shows the flow of studies through the review. The primary searches identified 6779 potentially relevant reports, 77 of which were selected for full text assessment. Two RCTs published in six reports [21-26] were included in the review. No non-randomised comparative studies were identified.

Characteristics of included studies

The two included RCTs [21,22] were both conducted in Norway and involved consecutively enrolled participants and prospective data collection. Table 1 presents demographic information for the two trials, which included a total of 201 participants at enrolment, all of whom were included in the statistical analyses. Participants' diagnosis was uncomplicated symptomatic gallstones (biliary pain only) [21] or acute cholecystitis [22]. Median age was 50 years (range 20 to 79 years) [21] and 58 years (range 27 to 77 years) [22]. Both trials enrolled some participants who had previously

presented to secondary care for gallstone disease: 30 participants (22%) [21] and 11 participants (17%) [22]. Both trials also reported the number of participants with concomitant diseases, specifically heart disease, diabetes and/or obstructive lung disease; in total, 16 participants (12%) [21] and 12 participants (19%) [22]. In both trials, the majority of participants were operated on via laparoscopic cholecystectomy (63.2% of participants in one trial [21] and 71% of participants in the other [22]). Median follow-up period was 14 years for both trials.

Table 1 Demographic information of included studies

	Schmidt 2011a [21]		**Schmidt 2011b [22]**	
	Surgery (n=68)	**Observation (n=69)**	**Surgery (n=31)**	**Observation (n=33)**
Sex				
Men (%)	13 (19%)	12 (17%)	14 (45%)	13 (39%)
Women (%)	55 (81%)	57 (83%)	17 (55%)	20 (61%)
Age				
Men (Median, range)	52 (27-74)	60 (30-79)	64 (41-77)	64 (29-73)
Women (Median, range)	52 (20-77)	48 (22-75)	58 (27-77)	47 (29-71)
Age Overall (Median, range)	50 (20-79)		58 (27-77)	
Diagnosis	Uncomplicated symptomatic gallstones (biliary pain only)		Acute cholecystitis	
Previous gallstones attacks (%)	64 (94%)	63 (91%)	NR	NR
Previous hospitalisation for gallstone disease (%)	14 (21%)	16 (23%)	11 (17%)	
Concomitant disease (heart disease/ diabetes/ obstructive lung disease) (%)	16 (12%)		12 (19%)	

Risk of bias

Risk of bias was judged as being low for all domains assessed for both trials. The summary figure is presented in Appendix 2.

Assessment of clinical effectiveness

Table 2 presents the findings of the two included studies and Table 3 a summary of the meta-analyses results.

A total of 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 less likely to have surgery (RR=0.50, 95% CI=0.34 to 0.73, p=0.0004), surgery-related complications (RR=0.36, 95% CI=0.16 to 0.81, p=0.01) or, more specifically, minor surgery-related complications (RR=0.11, 95% CI=0.02 to 0.56, p=0.008) than those randomised to surgery. In addition, participants randomised to observation were significantly more likely to experience gallstone-related complications (RR=6.69, 95% CI=1.57 to 28.51, p=0.01), in particular acute cholecystitis (RR=9.55, 95% CI=1.25 to 73.27, p=0.03). For 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 (chi^2=9.10, p=0.0026) and 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 percent 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.

Table 2 Findings of included studies

	Schmidt 2011a [21] (n=137) Uncomplicated symptomatic gallstones (biliary pain only)				Schmidt 2011b [22] (n=64) Acute cholecystitis			
	Observation (n=69)		Surgery (n=68)		Observation (n=33)		Surgery (n=31)	
	5 years	14 years	5 years	14 years	5 years	14 years	5 years	14 years
No. patients undergoing surgery	35/69 (51%)	35/69 (51%)	60/68 (88%)	60/68 (88%)	10/33 (30%)	11/33 (33%)	27/31 (87%)	27/31 (87%)
Pain attacks	NR	23/69 (33%)	NR	8/68 (12%)	NR	3/33 (9%)	NR	4/31 (13%)
Gallstone-related complications [a]	3/69 (4%)	3/69 (4%)	1/68 (1%)	1/68 (1%)	13/33 (39%)	11/33 (33%)	3/31 (10%)	1/31 (3%)
Acute cholecystitis	1	1	0	0	9	8	1	0
CBD stones	2	1	0	0	4	3	1	1
Acute pancreatitis	0	1	1	1	0	0	1	0
Surgery-related complications	5/69 (9%)	NR	10/68 (15%)	NR	2/33 (9%)	NR	9/31 (32%)	NR
Intra-abdominal infection/ bile leakage	3		2		1		1	
Wound infection/dehiscence	1		1		0		0	
Bile duct injury	0		0		0		1	
Re-operation								
Minor complications	1		1		0		0	
	0		6		1		7	

	Schmidt 2011a [21] (n=137) Uncomplicated symptomatic gallstones (biliary pain only)				Schmidt 2011b [22] (n=64) Acute cholecystitis			
	Observation (n=69)		Surgery (n=68)		Observation (n=33)		Surgery (n=31)	
	5 years	14 years	5 years	14 years	5 years	14 years	5 years	14 years
Admission due to gallstone-related pain	12/69 (17%)	NR	2/68 (3%)	NR	4/33 (12%)	NR	3/31 (10%)	NR
Mortality	NR	8/69 (12%)		11/68 (16%)	0/33 (0%)	8/33 (24%)	4/31 (13%)	10/31 (32%)
Further surgical intervention needed	NR	NR	NR	4/68 (6%) ERCP (CBD stone in 1)	NR	NR	NR	NR
Median time to surgery (months) from randomisation	NR	28	NR	3 (0-168)	NR	NR	3.6 (0.5-12.8)	4 (1-13)

[a]For the 14-year data, events that took place before surgery in the group randomised to cholecystectomy were not considered, unless as a result of dropout from surgery.

Table 3 Summary of meta-analyses results

Event	Observation n/N (%)	Surgery n/N (%)	Risk ratio [95% CI] Observation versus Surgery	Test for overall effect (p value)
Undergoing surgery (14y)	46/102 (45%)	87/99 (88%)	0.50 [0.34, 0.73]	0.0004
Pain attacks (14y)	26/102 (25%)	12/99 (12%)	1.62 [0.43, 6.17]	0.48
Admission due to gallstone-related pain (5y)	16/102 (16%)	5/99 (5%)	2.69 [0.57, 12.68]	0.21
Mortality (14y)	16/102 (16%)	21/99 (21%)	0.73 [0.41, 1.31]	0.30
Gallstones-related complications (All 14y)				
Total	14/102 (14%)	2/99 (2%)	6.69 [1.57, 28.51]	0.01
Acute cholecystitis	9/102 (9%)	0/99 (0%)	9.55 [1.25, 73.27]	0.03
CBD stones	4/102 (4%)	1/99 (1%)	2.86 [0.47, 17.59]	0.26
Acute pancreatitis	1/102 (1%)	1/99 (1%)	0.99 [0.06, 15.44]	0.99
Surgery-related complications (All 5y)				
Total	7/102 (9%)	19/99 (20%)	0.36 [0.16, 0.81]	0.01
Intra-abdominal infection/bile leakage	4/102 (4%)	3/99 (3%)	1.30 [0.30, 5.63]	0.73
Wound infection/dehiscence	1/102 (1%)	1/99 (1%)	0.99 [0.06, 15.44]	0.99
Bile duct injury	0/102 (0%)	1/99 (1%)	0.31 [0.01, 7.42]	0.47
Re-operation	1/102 (1%)	1/99 (1%)	0.99 [0.06, 15.44]	0.99
Minor complications	1/102 (1%)	13/99 (13%)	0.11 [0.02, 0.56]	0.008

Note: a risk ratio less than one favours observation.

Outcomes according to actual treatment received

In both included studies, some participants actually received the treatment other than the one to which they were randomised. For most outcomes, there was a marked shift as people switched to have surgery from the group randomised to conservative management. At the 5 year follow-up, 19% of those randomised to conservative management had been admitted to hospital for gallstone-related pain, whereas this figure was only 7% for people who were actually managed conservatively. Similarly, at the 14 year follow-up, 25% of the group randomised to conservative management had reported pain attacks, whereas this was only 12% for the group actually managed conservatively. At both intermediate and longer term follow-ups, acute cholecystitis was reported almost exclusively in the group randomised to conservative management. However, levels of acute cholecystitis were

similar for the two actual treatment groups. There was a similar pattern of change for incidence of CBD stones.

Cost effectiveness

The economic model was developed using evidence synthesis from three main sources: the systematic review and meta-analysis of clinical effectiveness, clinical opinion and a prior health state valuation survey [27]. The economic model compared cumulative costs and QALYs for a cohort of 51-year old women for a 5-year time horizon for two treatment strategies, conservative management and surgery. The results did not markedly change if a longer term horizon was adopted.

Table 4 presents the results for the base case analysis for a hypothetical cohort of people with symptomatic gallstones.

Table 4 Base case analysis

Strategy	**Costs (£)**	**Incremental cost**	**QALYs**	**Incremental QALYs**	**ICER [a] (£)**
Conservative Management	1104		4.139		
Surgery	2340	1236	4.232	0.094	13205
Probability cost-effective for different threshold values for society's willingness to pay for a QALY					
	£10,000	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Conservative Management	60%	51%	46%	44%	42%
Surgery	40%	49%	54%	56%	58%

[a] ICER = Incremental Cost-Effectiveness Ratio

On average, surgery cost £1,236 more than conservative management (i.e. average cost difference per patient over the five year follow up period). However, surgery was, on average, more effective, and generated 0.094 additional QALYs. The incremental cost per QALY was £13,205. The incremental cost-effectiveness result indicated that conservative management had a 51% chance of being considered cost-effective at society's willingness to pay threshold of £20,000. The probability of cost-effectiveness was not sensitive to changes in willingness to pay; when the threshold increased to £30,000, conservative management had a 46% chance of being considered cost-effective. Analysis performed using a cohort of 51 year old men had lower QALYs (conservative management 4.108 and cholecystectomy 4.21) but the incremental cost-effectiveness ratio (ICER) was similar to that of the base case analysis (ICER £12,178).

To account for the uncertainty surrounding the ICER (for surgery versus conservative management) resulting from the joint uncertainty surrounding all the model input parameters, probabilistic sensitivity analysis using Monte Carlo simulations was performed. The results of the probabilistic analysis are reported in the form of cost acceptability curves (Figure 2). Conservative management had a higher probability of being considered cost-effective for thresholds below £20,000 and surgery had a higher probability of being considered cost-effective as the threshold increased beyond £20,000.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the economic model. Full details are available from the authors on request.

A sensitivity analysis of the probability of people in the conservative management strategy needing surgery showed that , on average, the cost of conservative management reduced to £694 when the probability was 25% leading to an ICER of £33,542 per QALY for the surgical strategy. The probability that conservative management would be considered cost-effective was between 56% and 61% (for willingness to pay for QALY values of £20,000 to £30,000, respectively). However, the ICER reduced to £4291 when the probability of surgery amongst those initially managed conservatively was increased to 75%. Therefore, the results were sensitive to the probability of the number of people in the conservative management strategy needing surgery.

A sensitivity analysis of the effect of varying the probability of surgical complications from 0.05 to 0.20 revealed an ICER of £13,739 when the probability of complications was 0.05 and £12,135 when the probability of complications was 0.2. This suggests that the model is robust to the changes in the probability of surgical complications.

The results were more sensitive to changes in the costs of conservative management. As there are no data to support the average number of visits people may have to primary or secondary care, various exploratory analyses were performed to assess the impact of additional inpatient stays for people in the conservative management strategy. As anticipated, as the number of inpatient stays (each year) for the group with persistent pain increased, the cost of the conservative management strategy increased, thereby reducing the cost difference between the two strategies. This led to a reduction of the ICER from £13,205 (no inpatient stay) to £1,253 (3 non elective inpatient short stays).

The results were most sensitive to the utility value that was used for people who were managed conservatively. Based on a previous valuation survey [27], for the base case analysis it was assumed

that the utility value was 0.71 amongst those with persistent symptoms and 0.80 amongst those with no persistent pain. As appropriate information on the number of pain attacks and their impact on quality of life was not available from the trials data, these values may be over or underestimated, and were therefore investigated in sensitivity analysis. The ICERs varied from £4,175 (with utility value at 0.60 for persistent symptoms) to conservative management dominating surgery when the utility value was assumed to be 0.90. The probability of conservative management being considered cost-effective ranged from 8% to 82% for society's willingness to pay thresholds of £20,000 to £30,000. With changes in the utility value of persistent symptoms from 0.60 to 0.90, the probability of surgery being considered cost-effective at willingness to pay threshold of £20,000 varied from 92% to 18%. The results were not sensitive to changes in the utility of complications associated with surgery. The results were not markedly sensitive to changes in the discount rates applied to both the costs and the benefits.

Discussion

The two good-quality RCTs identified in the current literature randomised a total of 201 participants with symptomatic gallstone disease to either cholecystectomy or observation. The majority of people randomised to receive surgery (88%) and approximately half of people randomised to observation (45%) eventually underwent cholecystectomy during the 14-year follow-up period. Few gallstone-related complications were experienced by symptomatic people randomised to observation, and it is likely that pain was the reason why they underwent surgery [23]. In accordance with previous published studies [13,14], most of the surgical procedures were performed during the first 5 years, with virtually no operations after 5 years.

Not all participants in the observation group required cholecystectomy or experienced severe complications during the long-term follow-up. Notably, 55% of people randomised to observation did not require an operation during the 14-year follow-up period. Twelve percent of people randomised to receive cholecystectomy did not undergo the scheduled operation probably due to minimal, tolerable symptoms. These findings are in line with those of early natural history studies in the current literature [13,28].

Overall, the proportion of people suffering from pain attacks was found to be not significantly different between randomised groups (25% in observation group versus 12% in surgery group). Pain attacks were observed more frequently in participants treated conservatively (26/102 people) than those who underwent surgery (12/99 people) and in participants with biliary pain only (23/69

people, 33%) rather than in those with an initial diagnosis of acute cholecystitis (3/33people, 9%). It is noteworthy that when comparisons were made according to the treatment received rather than randomisation, pain episodes were similar amongst those treated conservatively (12/68, 18%) and those who were eventually operated on (26/133, 20%).

These findings on pain attacks are broadly similar to those in the clinical literature, which suggest that cholecystectomy is not always successful in relieving symptomatic people from pain. Up to 40% of people have been reported to experience post-cholecystectomy symptoms [29], which may persist or arise *de novo* after surgery [30]. Marked biliary pain has been described in 4-9% of people after cholecystectomy while persistent abdominal pain or non-specific pain has been reported in about 13%-37% of people [26,31-35]. Some investigators have also observed a persistent pain similar to that experienced pre-operatively in approximately 20% of people after cholecystectomy [36,37].

Although the majority of people treated conservatively (86%) did not experience gallstone-related complications, significantly more people randomised to observation (14%) than to surgery (2%) did experience events related to gallstone disease. New events that occurred in the observation group were acute cholecystitis, common bile duct stones and acute pancreatitis and they were observed more frequently in people with an initial diagnosis of acute cholecystitis (27%) than in those with biliary pain only (1%). Overall, few people experienced common bile duct stones or acute pancreatitis during the 14-year follow-up, with no significant difference between intervention groups. These findings are consistent with those of natural history studies which report a cumulative rate of 2 to 6% for common bile duct stones or acute pancreatitis in people observed for up to 10 years [15,38].

As expected, the risk of surgery-related complications was significantly higher among participants randomised to cholecystectomy. Twenty percent of participants randomised to surgery compared with 9% participants randomised to observation (who were eventually operated on) experienced surgery-related complications. Complications of cholecystectomy have been well documented and the findings of our two RCTs are consistent with those of recent Cochrane systematic reviews, which indicate that the total number of people suffering complications after open, small incision or laparoscopic cholecystectomy is high with no significant differences between the three surgical procedures [39-41].

There were no deaths caused by gallstone disease in the included trials. The all-cause mortality at 14 years was greater (but not significantly greater) among participants randomised to surgery. Notably, no significant differences between intervention groups were detected but the risk ratio was 0.73 (95%CI 0.41 to 1.31), favouring participants in the observation group. This finding suggests that people undergoing surgery had an increased probability of death compared with non-operated people. A clear explanation of this finding it is not immediately forthcoming. However, surgery in itself carries an intrinsic mortality risk, probably due to pre-existing co-morbidities.

Cost effectiveness

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 does show, however, that conservative treatment/observation fails to become a cost-effectiveness option when a high proportion of people develop complications and require emergency surgery. A policy of surgery for all, as opposed to a policy of conservative management followed by surgery amongst people whose symptoms persist, is likely to be more costly but more effective. However, due to the current dearth of evidence for some of the relevant health states for gallstone disease and, consequently, the uncertainty around some utility values used in the model, this conclusion is highly tentative.

Strengths and limitations of the review

We identified only two RCTs from the same investigators (published in six reports) and no non-randomised comparative studies. Both trials, even though at low risk of bias, were of small sample size and it is likely that they were underpowered to detect some important treatment differences between the interventions. Moreover, as a consequence of the small number of participants, few events were available for some of the analyses with wide confidence intervals around the estimates of treatment effect. Although statistical heterogeneity was not identified in the performed meta-analyses, the small sample sizes may have contributed to a lack of power to detect statistical heterogeneity. Nonetheless, despite the above limitations, it is clinically interesting that, after 14 years, 55% of participants randomised to observation and 12% of those randomised to surgery were not operated on and were safe in terms of adverse events.

A further limitation is that both trials were conducted outside the UK and it is likely that their findings cannot be easily generalised to a UK clinical setting. Conservative management is not a policy that is (or has been) used in the UK NHS and, until prospective data are collected, the exact

structure of a “conservative management strategy” in the UK NHS is unknown. This uncertainty affects both the costs and utility values. For example, there is a need for a prospective follow-up of people who do not have surgery to have further insight regarding their health seeking behaviour. Of particular interest are the number of times people visit their general practitioner, and other health care providers, for the management of uncomplicated symptomatic gallstone disease (biliary pain or cholecystitis). Similarly, a better insight into changes in health related quality of life is required, for example through prospective follow-up of people both before and after surgery.

A major challenge in analysing and presenting the results of the included trials was the number of participants in the observation group who crossed over to receive surgery and similarly, although less numerous, the number of participants in the surgery group who did not undergo the operation. We analysed the outcomes using an intention-to-treat approach (i.e. according to randomisation), which allows a proper comparison between treatment groups. However, when the number of participants who did not adhere to the intervention to which they were originally allocated is so high, the overall validity of the results becomes questionable and their interpretation problematic. For this reason we decided to also use an efficacy approach, which has the advantage of comparing the specific effects of surgery versus those of pure observation. However, it does violate randomisation and potentially introduce biases.

Conclusions and recommendation

Approximately 70,000 cholecystectomies are performed every year in the UK, the majority laparoscopically [42]. However, surgery could be avoided in a proportion of people with symptoms but no complications and this option appears to be safe in terms of subsequent events. The implications of our findings in terms of planning the best care pathway for people suffering from gallstone disease are therefore crucial. In particular, our findings highlight the importance of identifying which characteristics of gallstone disease could predict the evolution of symptoms. Therefore, it would be important to be able to identify people with uncomplicated symptomatic gallstones who could be treated conservatively. Unfortunately, at present, no definitive factors have been identified and symptoms of gallstone disease are still not completely understood, leaving it difficult to identify people who could benefit from a more conservative management approach. Furthermore, people vary considerably in the way they report their symptoms, and this may depend largely on individual pain threshold as well as personal preference for having or avoiding surgery. At present, in many cases, surgery is offered independently from the clinical symptoms of people

presenting with gallstone disease and without considering the potential benign course of the disease partly due to the wide diffusion of laparoscopic cholecystectomy.

There is now an indication too that removal of the gallbladder may lead to a slightly increased risk of colon cancer in women in the long term [43,44], although this will prevent the development of cancer of the gallbladder.

All of the above uncertainties indicate that a large, good quality, clinical trial is needed to compare the effects and safety of conservative management with cholecystectomy in people presenting with uncomplicated symptomatic gallstones (biliary pain only) or cholecystitis. Ideally, such a trial would be multicentre, with long-term follow-up and would include a pre-specified assessment of people's symptoms, relevant outcome measures, such as post-cholecystectomy symptoms and quality of life measurements, and a full economic evaluation.

Disclosures

The authors (Drs. Brazzelli, Cruickshank, Ahmed & Avenell; Profs McNamee & Ramsay; Ms Kilonzo; Ms Stewart; MsFraser; and Mr Elders) have no conflicts of interest or financial ties to disclose.

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Appendix 1: Sample search strategy

Ovid multifile search URL: http://shibboleth.ovid.com/

1. cholecystitis/
2. cholecystitis, acute/
3. cholecystolithiasis/
4. gallstones/
5. cholelithiasis/
6. biliary colic/
7. (gall?bladder adj3 (empyema or inflam$)).tw.
8. (biliary colic or gall?stone$ or cholecystitis or cholecystolithiasis).tw.
9. ((pain or biliary symptom$) adj5 (cholecystitis or cholecystolithiasis or gall?bladder)).tw.
10. or/1-9
11. exp Cholecystectomy/
12. cholecystectom$.tw.
13. ((excis$ or remov$) adj4 gall?bladder).tw.
14. ((surgery or surgical) adj5 (cholecystitis or cholecystolithiasis or gall?bladder)).tw.
15. or/11-14
16. exp clinical trial/
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomi?ed.ab.
20. randomly.ab.
21. trial.ab.
22. placebo.ab.
23. drug therapy.fs.
24. groups.ab.
25. comparative study/ use prmz
26. (prospective$ or retrospective$).tw.
27. (compare$ or compara$).ti,ab.
28. or/16-27
29. 10 and 15 and 28
30. (review or editorial or case report$ or letter).pt.
31. exp animals/ not humans/
32. 29 not (30 or 31)
33. limit 32 to yr="1980 -Current"
34. limit 33 to yr="2000-Current"
35. limit 33 to yr="1980-1999"
36. remove duplicates from 34
37. remove duplicates from 35
38. 36 or 37

Appendix 2: Risk of bias summary figure for clinical effectiveness review