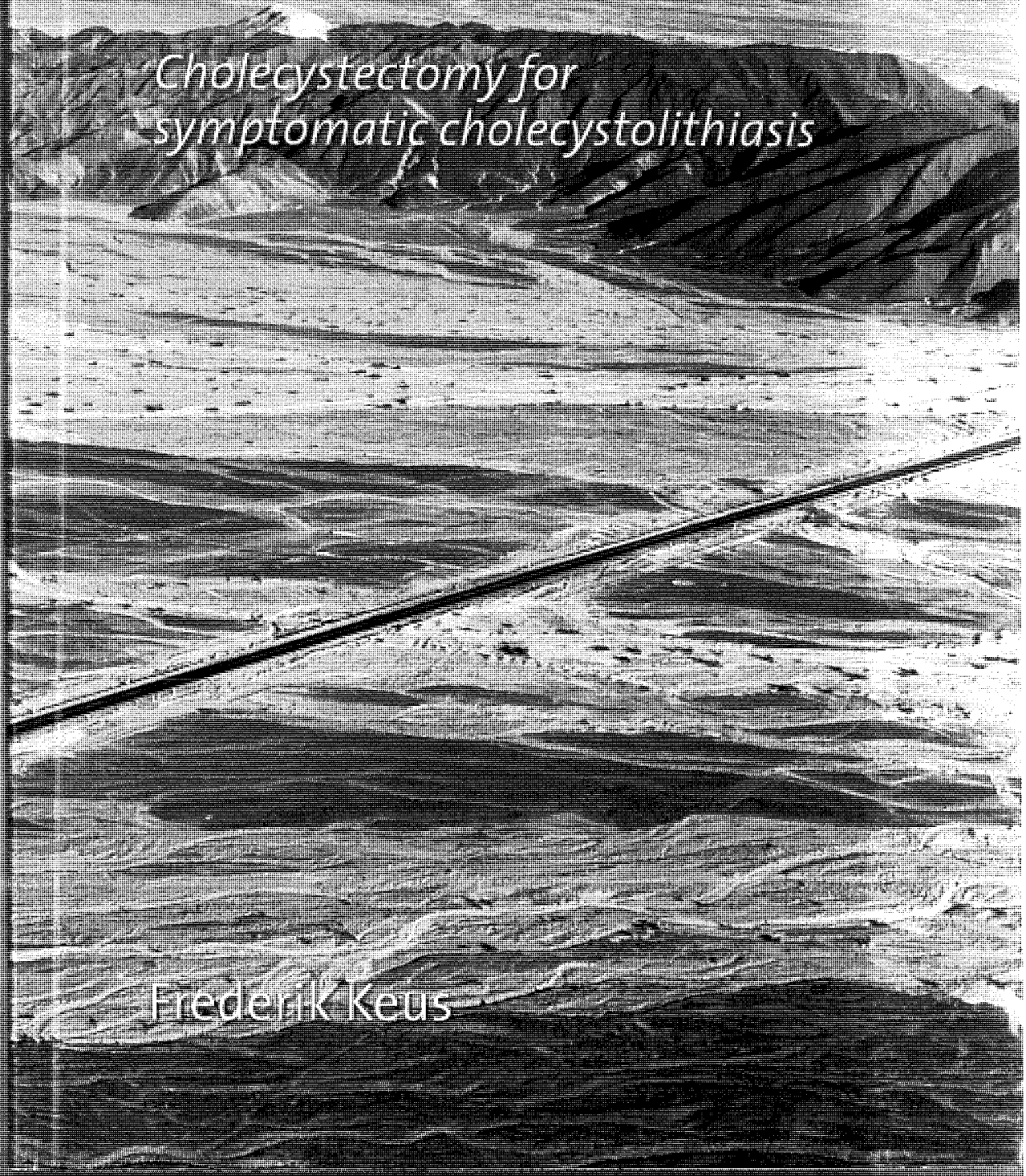
Evidence-based clinical intervention research

Cholecystectomy for symptomatic cholecystolithiasis



Frederik Keus

Nasca, Peru. *Located to the west of the Andean foothills, situated at approximately 500 meters above sea level there is a desert strip along the Pacific coast of Peru. The area has one of the driest climates on earth with only 15 minutes of rainfall each year. Standing on the ground there are rocks and stones, and a large emptiness as far as one can look. There is just nothing to see.*

One has to take an airplane and take off. Once into the air we look down at an enigma: more than 1000 figures covering more than 1000 square kilometers. Vast tracings of birds, animals and plants; a man 100 meters tall with owl-like eyes, his arm raised beckoning to us from a hillside; a huge bird, 274 metres long with a zig-zag neck running half the length of its body; dozens of spirals, triangles, zig-zags and trapezoids, and thousands of mile-long straight lines crisscrossing the dry wasteland, these geoglyphs have hitherto defied explanation. From the air the desert looks like a gigantic blackboard at the end of a busy day at school.

Dating of materials indicate that the lines are over 2000 years old. With no dust or sand to cover the plain and little rain or wind to erode it, lines drawn here tend to stay drawn. Lines are as narrow as the width of a boot varying to a giant trapezoid 90 meters wide, all perfectly formed. If the people who lived here 2000 years ago had no technology, how did they manage to construct such precise figures?

Nasca - called the Eighth Wonder of the World - has challenged all explanations. Until today, we have no clue how and why these drawings were made. Theories vary from runways for alien visitors, a map of the world, to constellations of the stars. Despite all our modern technologies we fail to explain the truth behind the mystery.

Clinical (intervention) research resembles Nasca. One needs to create distance to be able to objectively observe what is really there. Standing on the ground we are biased and there are risks of errors as we find ourselves to close to the object we want to observe making us unable to see the Nasca figure. The risks of errors need to be reduced by creating distance. A bird's eye perspective provides a three-dimensional distant view enabling us to see the figure depicting the truth. In clinical intervention research the three dimensions of systematic error, random error, and design error may facilitate a clear three dimensional view at the truth like in Nasca.

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Dolf Heebing

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Cholecystectomy for symptomatic cholecystolithiasis

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

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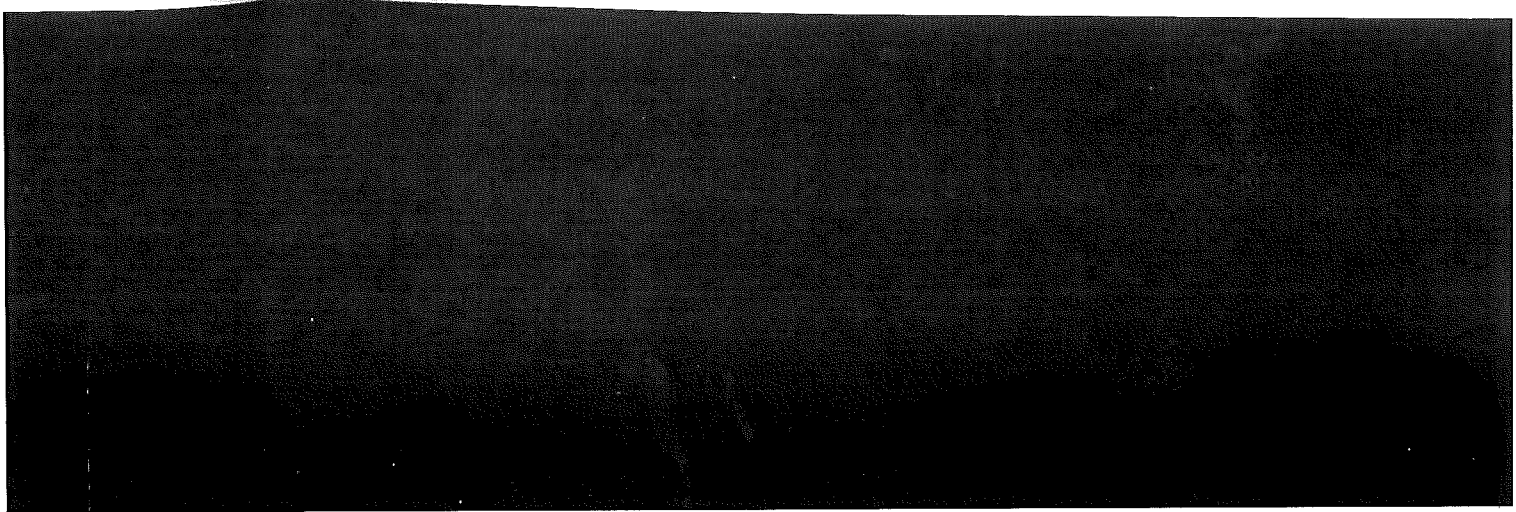
door

Frederik Keus
geboren op 15 oktober 1972
te Almelo



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Cholecystectomy for symptomatic cholecystolithiasis

An academic essay in
Medical Sciences

Doctoral Thesis

to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. S. C .J. J. Kortmann,
according to the decision of the Council of Deans
to be defended in public on Wednesday November 10, 2010
at 11.00 hours

by

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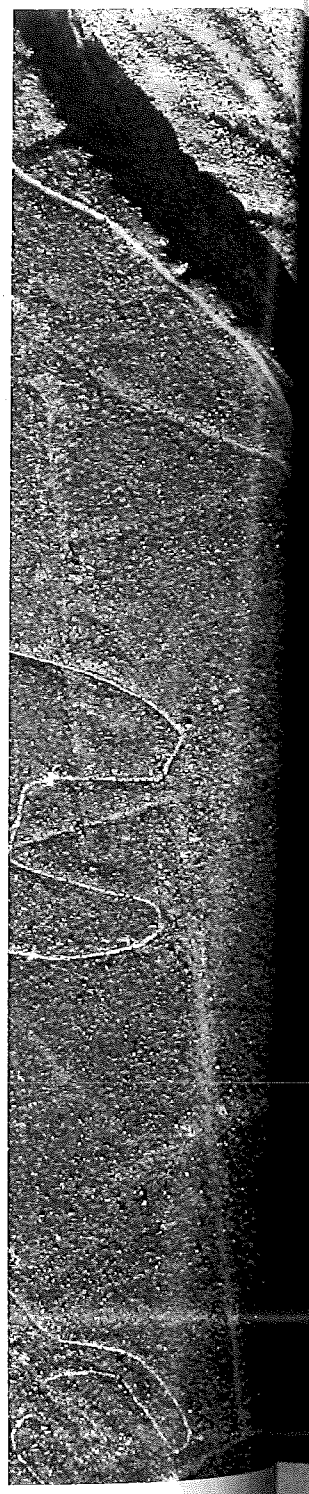


1

Introduction

In many people gallstones are present without symptoms and no treatment is needed. Only in the minority of people gallstones become symptomatic requiring treatment. Gallstone disease has a high prevalence and a high economic impact in civilized Western countries. Prevalence of gallstones in USA varies between 5–22% and depends on factors like age, sex, and race. The total estimated number of people with gallstones in USA is 20 million (290 million inhabitants). Prevalence data from European countries show similar distributions, resulting in a rough prevalence varying between 25-50 million people (503 million inhabitants in 32 countries).

In the USA about 600,000 cholecystectomies are performed annually and the annual estimated overall cost is more than $5 billion. For Europe no overall data are known, but based on the annual cholecystectomy rates between 1.13 per 1000 (Northern Europe) to 2.17 per 1000 inhabitants (USA) probably between 700,000-1,100,000 cholecystectomies are carried out. Gallstones are therefore one of the most common and most costly digestive diseases.

Carl Langenbuch performed the first cholecystectomy in humans in Berlin in 1882. Removal of both the gallstones and the gallbladder remains the principle of treatment today, because it removes the organ that contributes to both the formation of gallstones and the complications ensuing from them.

During a century, operative outcomes of traditional open cholecystectomy have consistently improved along with general advances in medicine. For over a century, the open cholecystectomy has been the gold standard and appeared to be a safe procedure with low complication rates. In uncomplicated procedures a hospital stay of three to five days is required and the largest drawbacks are the resulting pain and weeks of disability.

During the 1970s and 1980s alternative therapies aiming for gallstone removal only (like dissolution, fragmentation, and extraction) have passed by and are barely applied anymore. The disadvantage of therapies that only eliminate the stones is that gallstones recur.

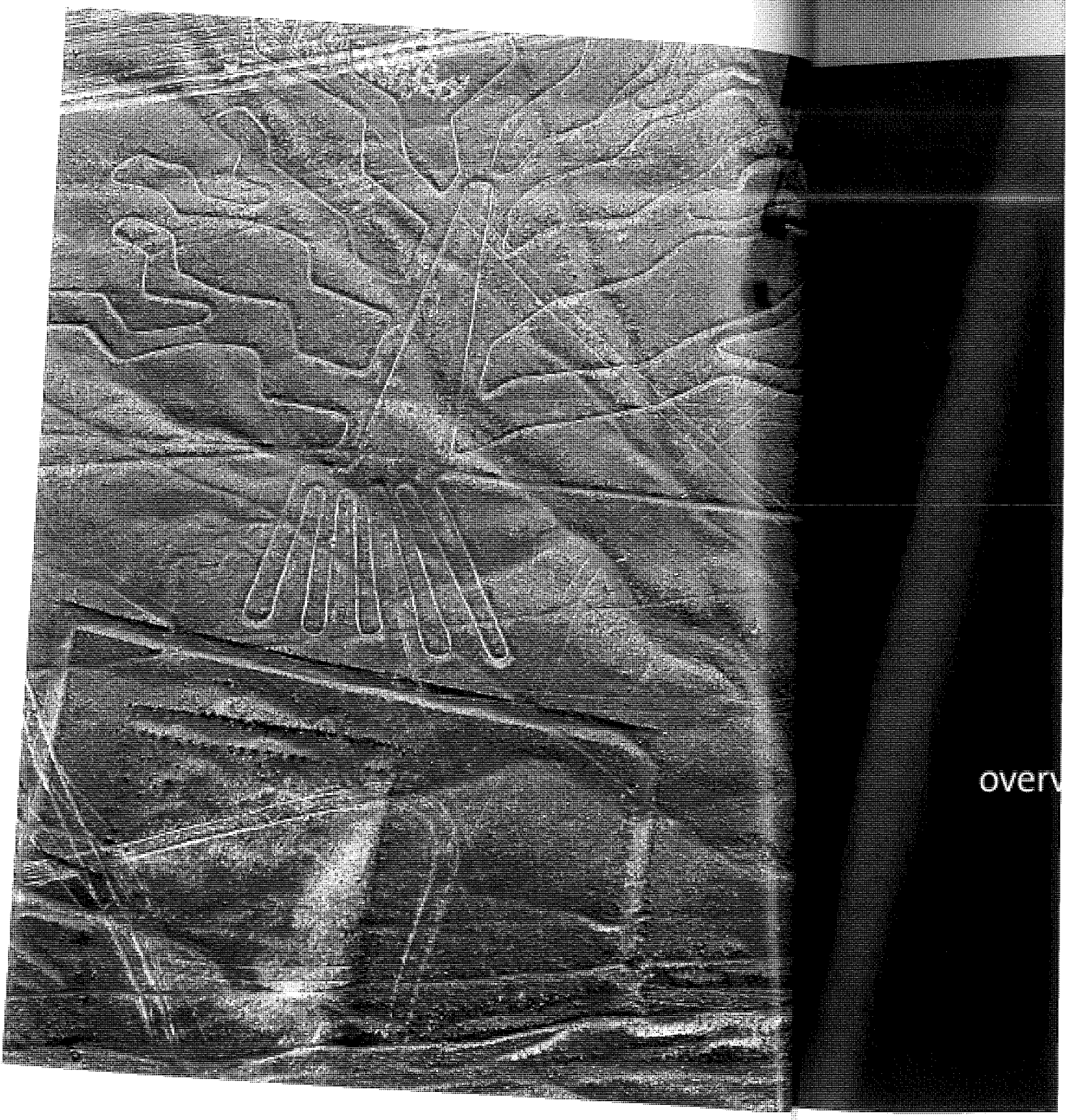
In order to reduce pain and enhance convalescence in traditional open cholecystectomy, incisions were shortened. During the 1970s the first small-incision cholecystectomy was described, aiming to reduce surgical trauma and quicken recovery. In case of technical difficulties, the incision is easily extended and converted into a traditional open cholecystectomy. During the 1980s more attention was drawn to this minimal invasive procedure and several series and alternative techniques were reported. However, further evaluation was interfered by another development at the end of the 1980s.

Mühe performed the first laparoscopic cholecystectomy in Germany in September 1985.

Although a surgical breakthrough, it did not gain much attention initially. Two years later a French gynaecologist inspired the French surgeons Dubois and Perissat who further developed the procedure. In the United States Reddick and Olsen further contributed to its enormous popularisation. Never before a new surgical technique was introduced and accepted as treatment of first choice in such a fast manner. Some declared that evaluation of the new laparoscopic technique would be unethical as superiority was considered obvious. Drawbacks of, especially initial, higher proportions of bile duct injuries were accepted and devoted to a learning curve. Already in 1993, within 5 years time, the laparoscopic cholecystectomy was declared to be the gold standard by a prestigious consensus conference without considering that a sufficient level of evidence for its superiority was not possible to be provided in such a short period of time.

Both the small-incision and the laparoscopic cholecystectomy are minimal invasive procedures aiming to reduce surgical trauma resulting in a quicker convalescence. Although nowadays surgical treatment and cholecystectomy in specific is difficult to conceive without laparoscopy, from a scientific point of view the true evidence of superiority of any of the three techniques is lacking. An evidence-based evaluation of cholecystectomy may help in the broad discussions on future needs and directions of surgical research and laparoscopy in specific.

In this thesis a matrix approach is developed to evaluate clinical intervention research on evidence-based principles. The clinical problem of surgical treatment of symptomatic cholecystolithiasis may serve as an example of clinical interventions. This thesis addresses two issues: the validity of the matrix approach for evidence-based clinical intervention research and the true evidence of (non-)superiority of either one of the techniques for cholecystectomy.



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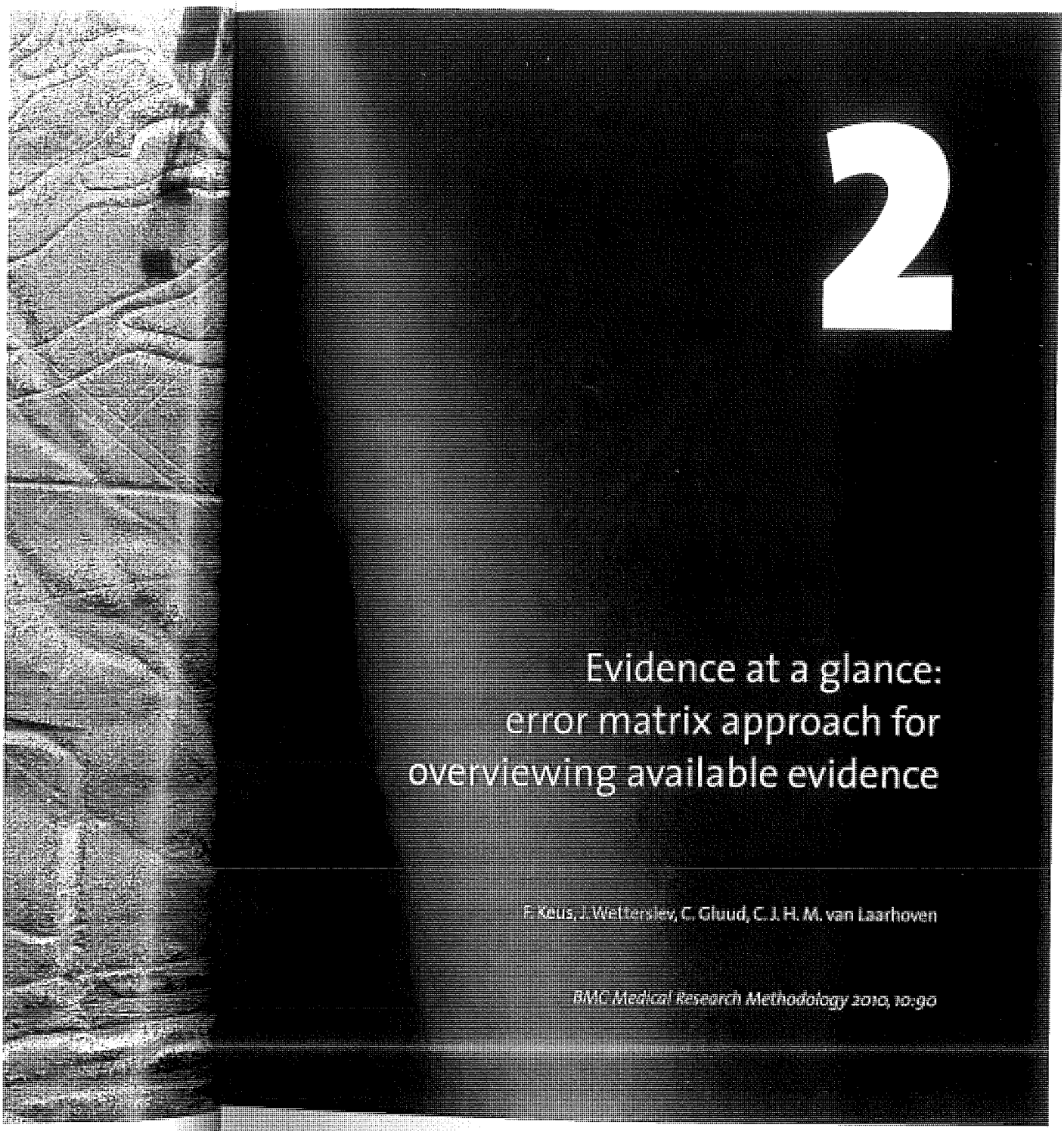

2

Evidence at a glance: error matrix approach for overviewing available evidence

F. Kaus, J. Wetterslev, C. Gluud, C. J. H. M. van Laarhoven

BMC Medical Research Methodology 2010, 10:90

ABSTRACT

Background

Clinical evidence continues to expand and is increasingly difficult to overview. We aimed at conceptualizing a visual assessment tool, i.e., a matrix for overviewing studies and their data in order to assess the clinical evidence at a glance.

Methods

A four-step matrix was constructed using the three dimensions of systematic error, random error, and design error. Matrix step I ranks the identified studies according to the dimensions of systematic errors and random errors. Matrix step II orders the studies according to the design errors. Matrix step III assesses the three dimensions of errors in studies. Matrix step IV assesses the size and direction of the intervention effect.

Results

The application of this four-step matrix is illustrated with two examples: peri-operative beta-blockade initialized in relation to surgery versus placebo for major non-cardiac surgery, and antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. When clinical evidence is deemed both internally and externally valid, the size of the intervention effect is to be assessed.

Conclusion

The error matrix provides an overview of the validity of the available evidence at a glance, and may assist in deciding which interventions to use in clinical practice.

Many consider evidence-based medicine (EBM) a paradigm shift in medicine. However, EBM should rather be considered a continuation of the way of thinking that evolved from rationalistic optimist philosophers like Thomas Kuhn and Karl Popper [5,6]. They introduced modern concepts of paradigm shift and critical rationalism and stressed the importance of scientific experiments or trials in order to challenge 'normal science' and gain reliable knowledge. EBM is part of this development, which is underpinned by the teaching that clinical knowledge based on randomized trials and systematic reviews of randomized trials represent the most reliable evidence [3,4]. In accordance, Sehon and Stanley [7] state that EBM should not be considered a Kuhnian paradigm shift [6], but should more readily be seen in the light of the 'Quinean doctrine of holism' [8]. The 'web of belief' metaphor of Quine integrates all fundamental different approaches and underlines the dependency of all alternative approaches on each other [7,8]. EBM rather provides categorization of results based on more or less controlled observations fitting in the 'web of belief'. Analogous to this, our presented matrix could be considered a helpful tool in categorizing evidence and providing graphical visualization. Although we recognize the value of alternative approaches in medicine, we consider that the solid ground, which EBM provides, is the approach with which to go forward. We strongly recommend against 'evidence shopping' for the evidence one may eventually find to support a prejudiced view, ignoring the possible lack of evidence at a higher level (that is jumping the fence where it is lowest). This seems reasonable both when best available evidence is present, but also when best obtainable evidence is within reach with some extra reasonable efforts.

Table 1

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BACKGROUND

Evidence-based medicine (EBM) was first introduced in 1992 [1], and its increased application is reflected among others by the growth of The Cochrane Library databases as well as implementation of evidence-based guidelines into clinical practice [2]. EBM underpins that information provided from randomized trials, and systematic reviews of randomized trials represent the most reliable evidence regarding intervention effects [3,4]. Thanks to the sustained scientific process (Table 1), we now know that the reliability of what we observe varies due to a whole array of different factors. There are three dimensions that particularly influence the reliability of our observations in clinical research and they are empirically and theoretically well accepted: the risk of systematic error ('bias'), the risk of random error ('play of chance'), and the risk of design error ('wrong design to answer the posed question') [4,9].

EBM usually follows a four-phase process starting from a clinical question proceeding to the implementation of new evidence (Figure 1) [3]. Phase 1 is the formulation of a research question and literature search strategy. Phase 2 is the subsequent systematic appraisal and synthesis of the available evidence. Phase 3 covers the initiation of new research. Alternatively, phase 4 is the implementation of all available evidence when statistically and clinically convincing evidence has been obtained.

In daily clinical practice, the question of whether sufficient evidence is available to recommend the implementation of a specific intervention as a treatment arises frequently [3]. Depending on the specific clinical question, often an exhaustive list of references is retrieved when using a sensitive search strategy in multiple databases [3]. After the selection of studies, their data must be interpreted [10-13].

Since results may be contradictory and studies may differ in more than one aspect, to draw a clear, practical conclusion from the publications may be problematic [14].

Objective

We aimed at conceptualizing a visual assessment tool, i.e., a matrix for overviewing studies and their data in order to assess the clinical evidence. The matrix is constructed from the three dimensions of errors: systematic error ('bias'), random error ('play of chance'), and design error ('wrong design to answer the question posed' or 'wrong context'). The application of this matrix will be illustrated by two examples: peri-operative beta-blockade initialized in relation to surgery versus placebo for major non-cardiac surgery, and antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.

METHODS

The three major error dimensions

The risk of systematic error ('bias')

When evaluating a clinical study, one should always try to assess its risk of systematic error [3,4,9-16]. There is increasing agreement on how trials and studies can be placed in a hierarchy when assessing the risk of systematic error [3,4,9-16], depending on the

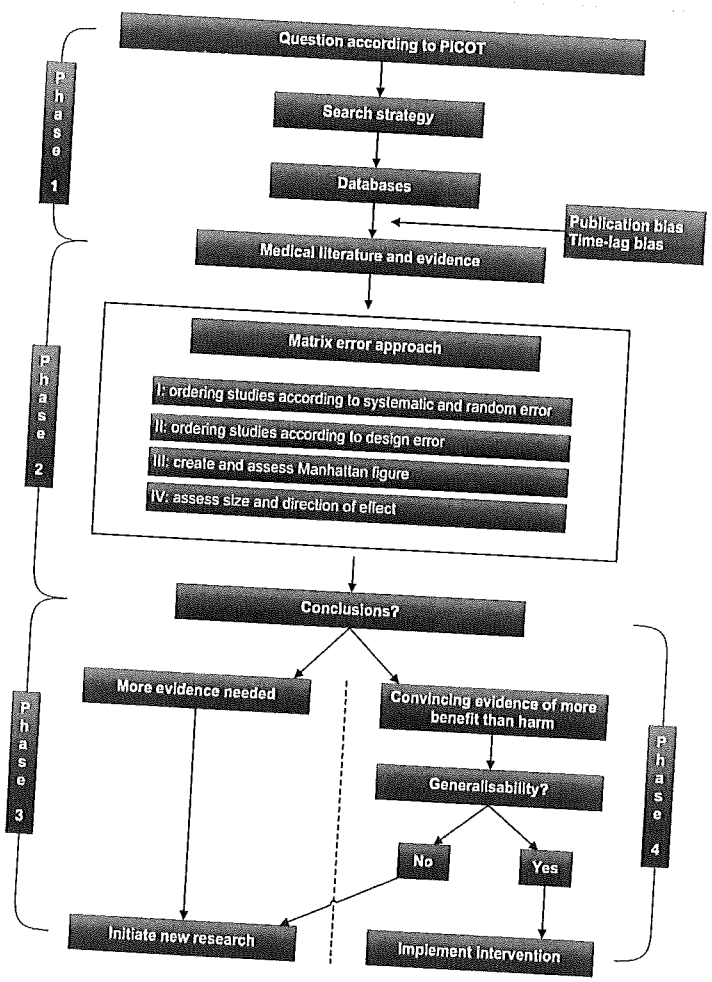

Figure 1: Overview of the four phases in the process of evidence-based medicine from question to the initiation of new research or implementation of new evidence.

PICOT: patients, intervention, control, outcome measure, time.

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Level 1c	Met
Level 1d	Ran
Level 2a	Met
Level 2b	Coh
Level 3a	Met
Level 3b	Cas
Level 4	Cas
Level 5	Exp

Table 2: Catego

type of research (therapeutic, diagnostic, etiologic, or prognostic) [3,10,11,17]. The risk of systematic error influences the reliability of observed intervention effects [3,10,11,18,19]. A significant association between inadequate or unclear bias protection and overestimation of beneficial effects and underreporting of adverse effects has been demonstrated [16,19-23]. Differences in risk of bias are found both between the different levels of evidence and within each level of evidence [4,16,20].

For randomized trials, there is empirical evidence that at least six components are associated with systematic error: generation of the allocation sequence [24], allocation concealment [25], blinding [26], incomplete outcome measure reporting [4], selective outcome measure reporting [4], and other bias mechanisms (e.g., baseline imbalance, early stopping, vested interests, etc.) [4,16,20,27-29]. The impact of early stopping of trials on bias is largely dependent on how the stopping rules were defined and the level of statistical significance of the interim analysis [30-32]. Trials with one or more systematic error components assessed as inadequate or unclear are considered to be of high risk of bias, while trials with all quality components assessed as adequate are considered to be of low risk of bias [15,27,33]. Trials with a low risk of bias are more likely to estimate the 'true' effect of the intervention [16,20,27,33].

The systematic error dimension can be measured by an ordinal variable expressed in the levels of evidence (Table 2).

The risk of random error ('play of chance')

The risk of random error is the risk of drawing a false conclusion based on sparse data. There are two types of false conclusions: a false rejection of the null hypothesis (type I error; alpha) or a false acceptance of the null hypothesis (type II error; beta). When data are sparse, then the so called 'intervention effect', whether beneficial or harmful, may

Category	Studies
Level 1a	Meta-analysis of randomized trials with low risk of bias
Level 1b	Randomized trial with low risk of bias
Level 1c	Meta-analysis of all randomized trials
Level 1d	Randomized trial with high risk of bias
Level 2a	Meta-analysis of cohort studies
Level 2b	Cohort study
Level 3a	Meta-analysis of case-control studies
Level 3b	Case-control study
Level 4	Case-series
Level 5	Expert opinion

Table 2: Categorization of systematic error (bias) of clinical intervention studies into levels of evidence.

in fact be caused by randomly skewed variation in prognostic factors between the intervention groups due to sampling error.

The question, however, is how we quantify and compare the risk of random error between different studies with varying numbers of participants. A p-value reflects the risk that the difference in outcome between two interventions has arisen by chance, given the data and the null hypothesis are true. Since random low (and random high) p-values occur, especially during accumulation of data and sequential testing, the p-value does not sufficiently reflect the true risk of random error. Therefore, the p-values of intervention effect estimates certainly are not suitable for comparison of the risk of random error between different studies [32,34-37]. We suggest using the standard error (SE) for the evaluation of the risk of random error. We used the statistical algorithms from the statistical methods group of the Cochrane Collaboration [38]. The SE in a study may be considered a measure of uncertainty. The SE measures the amount of variability in the sample mean; it indicates how closely the population mean is likely to be estimated by the sample mean. The size of the standard error depends both on how much variation there is in the population and on the size of the sample. When two independent proportions $p_1 = a/n_1$ and $p_2 = c/n_2$ (with *a* and *c* being the numbers of patients with events, *b* and *d* being the numbers of patients with no events, and n_1 and n_2 being the total numbers of patients in the intervention group and control group, respectively) are considered in an individual study or a trial *i*, then the relative risk (RR_i) is defined by:

$$RR_i = \frac{p_1}{p_2}$$

The SE of the log risk ratio for an individual study is calculated by the following formula:

$$SE\left[\ln\left(RR_i\right)\right] = \sqrt{\frac{1}{a_i} + \frac{1}{c_i} - \frac{1}{n_{1i}} - \frac{1}{n_{2i}}}$$

The Peto odds ratio ($OR_{peto,i}$) for an individual study or trial *i* is defined by:

$$OR_{Peto,i} = \exp\left[\frac{Z_i}{V_i}\right]$$

where

$$Z_i = a_i - E\left[a_i\right] = a_i - \frac{n_{1i}(a_i + c_i)}{N_i} \quad \text{and} \quad V_i = \frac{n_{1i} \cdot n_{2i} \cdot (a_i + c_i) \cdot (b_i + d_i)}{N_i^2 \cdot (N_i - 1)}$$

The SE of the log Peto odds ratio for an individual study is defined by:

$$SE\left[Ln(OR_{Peto,i})\right] = \sqrt{\frac{1}{V_i}} \quad \text{or} \quad SE\left[Ln(OR_{Peto,i})\right] = \frac{N_i\sqrt{N_i - 1}}{\sqrt{n_{1i} \cdot n_{2i} \cdot (a_i + c_i) \cdot (b_i + d_i)}}$$

In a meta-analysis results of studies or trials are meta-analysed into one intervention effect estimate. For the Mantel-Haenszel pooled risk ratio (RR_{MH}) the natural logarithm of the RR_{MH} has the standard error given by:

$$SE[\ln(RR_{MH})] = \sqrt{\frac{P}{R \cdot S}}$$

where

$$P = \sum_i \frac{n_{1i} \cdot n_{2i} \cdot (a_i + c_i) - a_i \cdot c_i \cdot N_i}{N_i^2} \quad \text{and} \quad R = \sum_i \frac{a_i \cdot n_{2i}}{N_i} \quad \text{and} \quad S = \sum_i \frac{c_i \cdot n_{1i}}{N_i}$$

and N_i being the total number of patients in a trial.

For the pooled Peto OR (OR_{peto}) the natural logarithm of the OR_{peto} has the standard error given by:

$$SE[Ln(OR_{Peto})] = \sqrt{\frac{1}{\sum V_i}}$$

SE depends on the numbers of events and the sample size.

Due to spurious results, incorrect type I error inferences may be drawn. Recent reports indicate that the influence of the 'play of chance' may be much larger than generally perceived [39]. In randomized trials, random error may be one reason for the early stopping of trials at interim analyses when benefit or harm appear to be significant [32,40]. Increased random error may also play a role in the repeated analyses of accumulating data in both trials and meta-analyses [36,41-44]. A cumulative meta-analysis subjects accumulating data to repeated testing of the data and is bound to eventually lead to a false rejection of the null hypothesis ('false positive' result) [45,46]. The random error phenomenon or 'multiplicity' also plays a role in the evaluation of secondary outcome measures [40]. For example, when data on the primary research outcome, on which the sample size calculation was based, may not show statistical significance, while another outcome measure, for which no separate sample size calculation was performed, exhibits statistical significance [47,48].

Random error may be expressed in a continuous variable using the standard error of for example the log of Peto odds ratios or the log of relative risks.

The risk of design errors (external validity) the participants included, the outcomes measured, the interventions, etc

When there is sufficient internal validity, i.e., low risks of systematic errors and random errors, it becomes relevant to consider the risks of design errors (external validity). The

design (or context) of any piece of research determines its external validity or generalisability (Table 3) [4]. The external validity becomes questionable when a wrong design has been used to answer the question posed. Among the many variables that should be considered, the relevance of different outcome measures are of central importance to clinical research [13]. We, therefore, focus on them from a patient's perspective.

Outcome measures can be divided into three categories according to the GRADE classifications (Figure 2) [13]. Primary outcome measures are central in deciding the use of one intervention over another. Large differences in the primary outcome measure between groups in a clinical trial may lead to early termination of a trial (following recommendations of a data safety and monitoring committee) [49]. Choice of the primary outcome should concur with the GRADE category of outcomes, 'critical for decision-making' [13]. Secondary outcome measures are additional outcome measures. If they are positively influenced by an intervention, the results may speak for recommending the intervention only if no clinically and statistically significant effects exist on the primary outcomes (e.g., a RR=1.00 with 95% confidence limits from 0.98 to 1.02). The secondary outcomes should concur with the second and third GRADE categories of 'important, but not critical outcomes' [10-13].

GRADE has schematically ordered outcomes according to patients' perspective on a categorical scale from 1 to 9, with the most critical outcome, mortality, being graded 9 [13]. Depending on the outcomes, this scale should sometimes be considered nominal and in other situations be considered functional. Moreover, the severity of each outcome may differ as well. A stroke can be minor, while a myocardial infarction may involve a substantial worsening of cardiac function. Grading of outcome measures may also vary according to the clinical question. Therefore, outcomes within a category (i.e., critical, important, or not important) may be interchangeable. However, one can hardly argue that outcomes between categories (i.e., critical, important, or not important) are interchangeable (e.g., mortality is always more important than length of stay in hospital).

1	Outcome measures
2	Participants
3	Experimental intervention
4	Control intervention
5	Clinical centres or settings including patients
6	Goal - explanatory or pragmatic
7	Trial structure - parallel group, crossover, etc
8	Objective - superiority, equivalence, non-inferiority
9	Unit of analysis

Table 3: Types of variables to consider when evaluating the risk of design errors ('context errors') and hence external validity of evidence.

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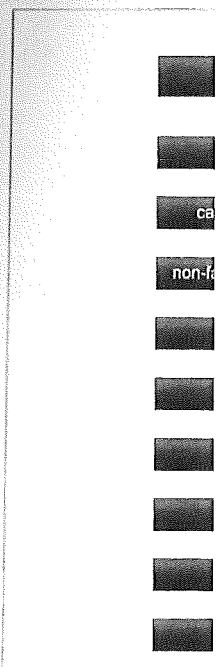

Figure 2: Hiera

Some outcome me

Eventually, the design error dimension can be expressed by the priority of outcome measures as an ordinal variable according to GRADE [13].

Conceptualization of the error matrix

A four-step matrix can be constructed, building upon the three dimensions: systematic error, random error, and design error. Matrix step I ranks the identified studies according to the dimensions of systematic errors and random errors. Matrix step II orders the studies according to the design errors. Matrix step III assesses the three dimensions of errors in studies. Here, a 'Manhattan-like' error matrix is constructed where the best evidence is represented by the largest skyscrapers located on the 'upper-west side'. Matrix step IV assesses the size and direction of the intervention effect, e.g., by calculating the number-needed-to-treat to obtain benefit or to harm one patient.

The principle of the matrix approach can be used in different situations. The overall effort in research should be to minimize all three risks of errors before the size and the direction of the intervention effect can be assessed reliably. The 'algorithm' of the matrix

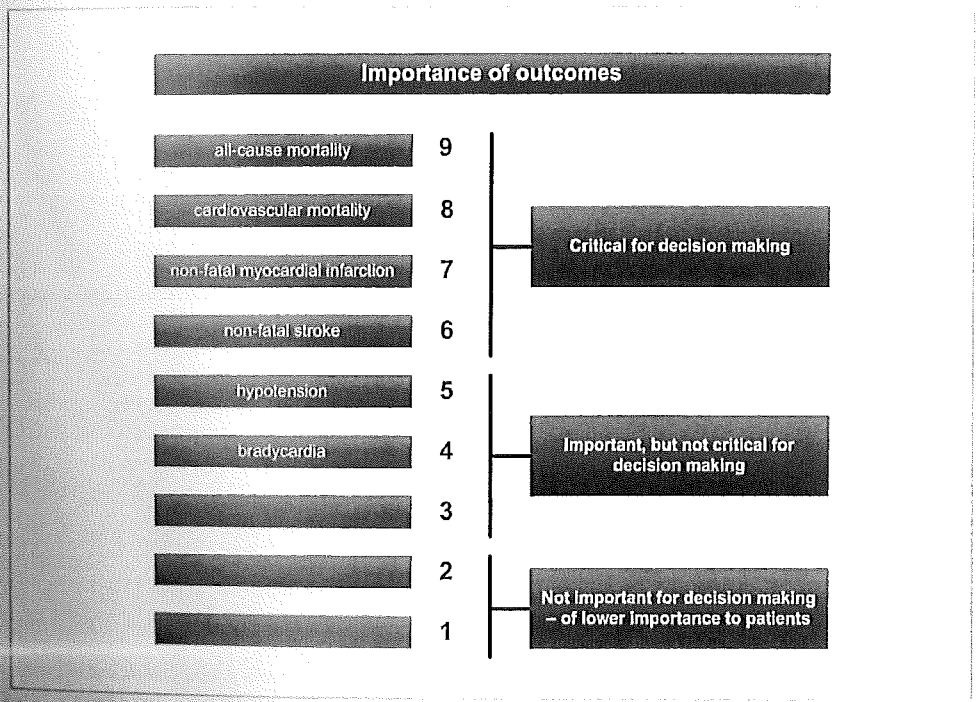

Figure 2: Hierarchy of outcomes according to importance to non-cardiac surgery patients undergoing preventive beta-blocker intervention [13].

Some outcome measures may be correlated (e.g. cardiovascular mortality is included in all-cause mortality).

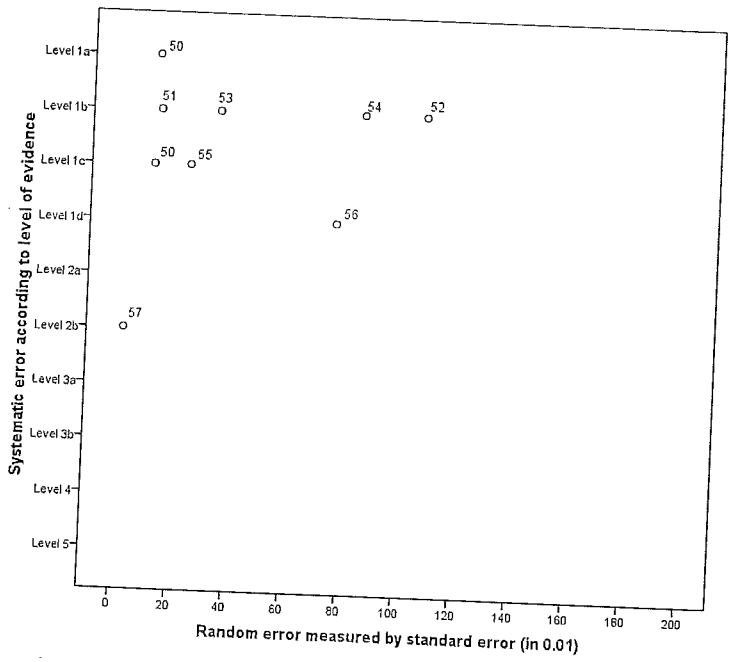

Figure 3: Matrix step I, ordering of evidence according to systematic error (in levels of evidence) and random error (measured by standard error) considering all-cause mortality in peri-operative beta-blockade versus placebo for major non-cardiac surgery (example 1).

	Level of evidence	Standard error			
		All-cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke
Bangalore [50]	1a	0.12	0.16	0.10	0.28
Poise [51]	1b	0.13	0.17	0.10	0.33
MaVS [52]	1b	1.07	Z	N	0.66
Dipom [53]	1b	0.34	0.48	0.91	Z
Mangano [54]	1b	0.85	1.22	1.22	1.11
Bangalore [50]	1c	0.11	0.15	0.09	0.28
Wetterslev [55]	1c	0.24	N	0.23	N
Poldermans [56]	1d	0.76	0.76	Z	N
Lindenauer [57]	2b	0.02	N	N	N
AHA Guidelines [58]	5	N	N	N	N

Table 4: Ordering of evidence according to levels of evidence (systematic error), standard error (random error), and outcome measures (design error) in peri-operative beta-blockade versus placebo for major non-cardiac surgery (example 1).

Z: outcome with zero-events in one or both treatment arms which makes SE incalculable; N: no data.
Some outcome measures may be correlated (e.g. cardiovascular mortality is included in all-cause mortality).
In this example the formulas for SE of $lnRR_i$ for individual studies and SE of $lnRR_{MH}$ for meta-analysis were used.

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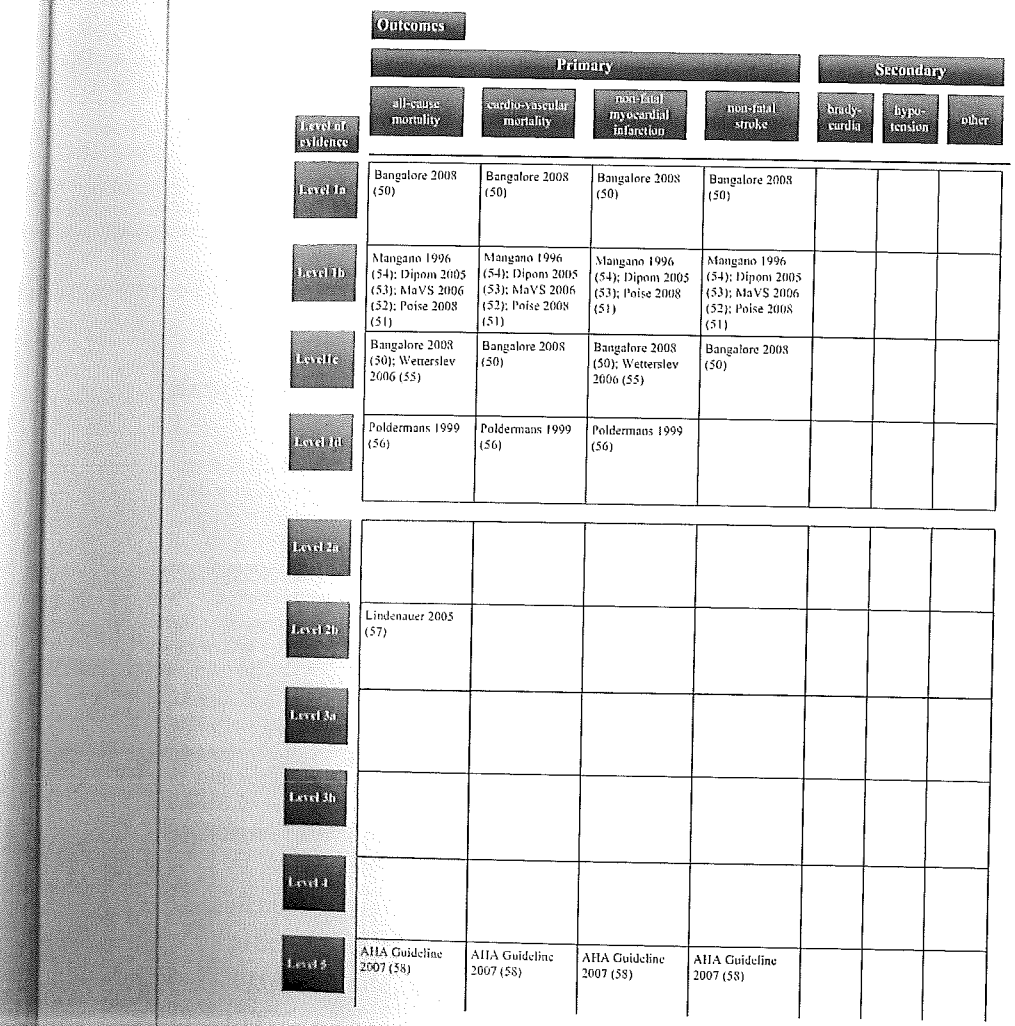
Figure 4: Matrix ste according to im

approach is generally applicable to all kinds of interventions, although details may differ according to the specific clinical question. Or, the character of the three dimensions remains the same, while according to the specific question details may differ, like: the preferred hierarchy for levels of evidence, the chosen formula for standard error (*RR*, OR_{peto}, or any other association metric), and the types of outcomes.



Level of evidence	Primary: all-cause mortality	Primary: cardio-vascular mortality	Primary: non-fatal myocardial infarction	Primary: non-fatal stroke	Secondary: brady-cardia	Secondary: hypo-tension	Secondary: other
Level 1a	Bangalore 2008 (50)	Bangalore 2008 (50)	Bangalore 2008 (50)	Bangalore 2008 (50)			
Level 1b	Mangano 1996 (54); Dipom 2005 (53); MaVS 2006 (52); Poise 2008 (51)	Mangano 1996 (54); Dipom 2005 (53); MaVS 2006 (52); Poise 2008 (51)	Mangano 1996 (54); Dipom 2005 (53); Poise 2008 (51)	Mangano 1996 (54); Dipom 2005 (53); MaVS 2006 (52); Poise 2008 (51)			
Level 1c	Bangalore 2008 (50); Wetterslev 2006 (55)	Bangalore 2008 (50)	Bangalore 2008 (50); Wetterslev 2006 (55)	Bangalore 2008 (50)			
Level 1d	Poldermans 1999 (56)	Poldermans 1999 (56)	Poldermans 1999 (56)				
Level 2a							
Level 2b	Lindenauer 2005 (57)						
Level 3a							
Level 3b							
Level 4							
Level 5	AHA Guideline 2007 (58)	AHA Guideline 2007 (58)	AHA Guideline 2007 (58)	AHA Guideline 2007 (58)			

Figure 4: Matrix step II, ordering of evidence on peri-operative beta-blockade versus placebo for major non-cardiac surgery according to importance of outcome measures (design error) and levels of evidence (systematic error) (example 1).

The outcome measures have been adapted to the beta-blockade question.

5a

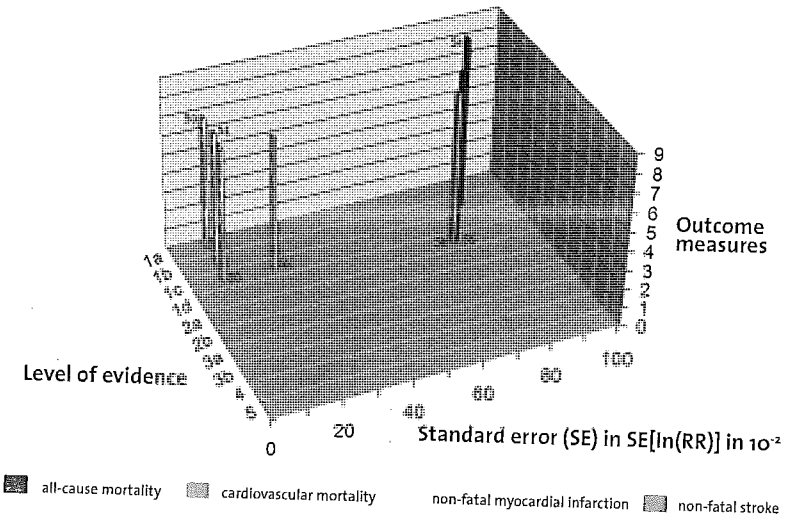


Figure 5a: Outcomes with benefit of peri-operative beta-blockade versus placebo.

Manhattan-like three-dimensional matrix building upon the risks of systematic error, random error, and design error. The evidence with the lowest systematic, random, and design error is represented by the tallest skyscrapers, located on 'the upper west side'.

A 'quick guide' to the perception of the figure:
If you want to know what the evidence is for peri-operative beta-blockade to influence myocardial infarction: go to the yellow bars and read 1) Level of evidence (the risk of systematic error) and 2) standard error (the risk of random error).

Data with risk of systematic error > level 2b and random error SE > 1.0 were omitted from the figure. The guidelines, which advocate the use of peri-operative beta-blockade, were not included in this figure since the systematic error is level 5 and the random error cannot be calculated (not based on data) [58]. The SE of outcomes with zero events cannot be calculated either.

From these 'benefit' and 'harm' Manhattan figures, one can see at a glance that beta-blockers may provide benefit to patients in terms of nonfatal myocardial infarction (yellow bars). However, one can also see that beta-blockers may cause harm to patients in terms of all-cause mortality (red bars), cardiovascular mortality (blue bars), and nonfatal stroke (green bars). Reading the dimension of systematic error it is immediately clear that there is level 1a evidence available for all these four outcome measures. Reading the dimension of random error on this systematic error level of evidence shows that there is a small risk of random error considering all-cause mortality (0,12), cardiovascular mortality (0,16), and nonfatal myocardial infarction (0,10), and a moderate risk of random error considering nonfatal stroke (0,28). It is clear at a glance that the best available evidence does not support peri-operative beta-blockade for major non-cardiac surgery.

0 to 0,10 = ignorable risk of random error
0,10 to 0,20 = small risk of random error
0,20 to 0,30 = moderate risk of random error
0,30 to 0,50 = substantial risk of random error
> 0,50 = high risk of random error

A clean version for creating a Manhattan figure can be obtained at the Copenhagen Trial Unit's homepage (www.ctu.rh.dk).

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RESULTS

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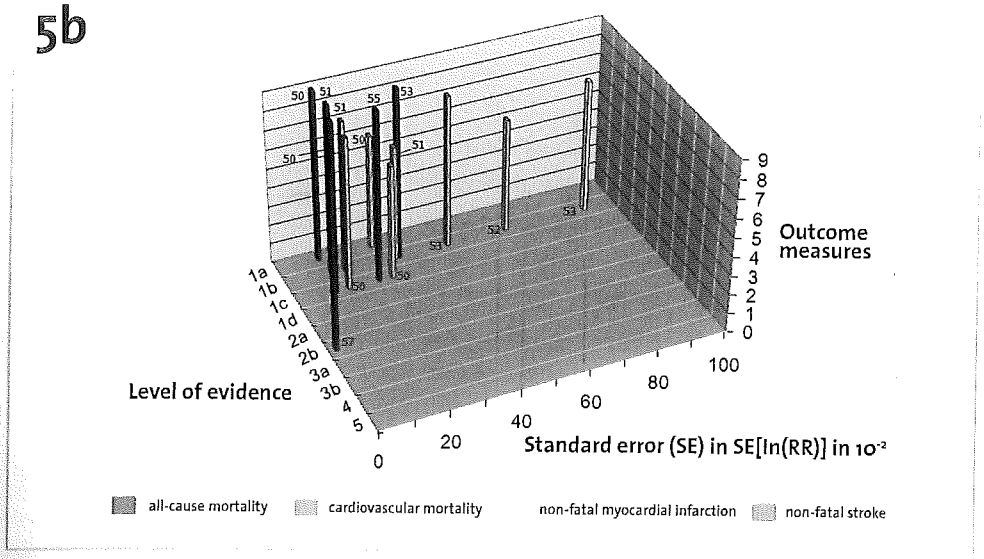

Figure 5b: Outcomes with harm of peri-operative beta-blockade versus placebo.

RESULTS

The application of this four-step matrix is illustrated with two examples: peri-operative beta-blockade initialized in relation to surgery versus placebo for major non-cardiac surgery, and antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.

Example 1: Initiating peri-operative beta-blockade for major non-cardiac surgery

A clinical question in PICOT structure illustrates this model. Is initiating peri-operative beta-blockade effective in patients undergoing major non-cardiac surgery?
Patients: patients undergoing major non-cardiac surgery; **I**ntervention: initiating peri-operative beta blockade; **C**ontrol: placebo; **O**utcome measure: mortality, myocardial infarction, and stroke; **T**ime: follow-up of at least 30 days.

We searched in CENTRAL in The Cochrane Library, PubMed, EMBASE, and personal files for all article types up to October 2009, in all languages. Specific searches using the terms 'beta-blockade', 'peri-operative', 'placebo', 'mortality', 'randomised', and 'non-cardiac surgery' were undertaken. The search resulted in multiple publications relevant to our question. References were selected from journals on the basis of importance and relevance [50-58]. We included the publications in our matrix evaluation by extracting information on all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. However, the matrix may easily be extended to other outcomes.

In step I, we assessed the systematic error and the random error for the chosen outcomes of each study (Figure 3, Table 4). In step II, we evaluated the design error (Figure 4). In step III, we constructed the three-dimensional matrix (Figure 5). We did not elaborate on the matrix step IV in this example.

From Figure 5 it can be concluded at a glance that peri-operative beta blockade does not reduce mortality in patients undergoing major non-cardiac surgery. Peri-operative beta-blockade in these patients seems to increase all-cause mortality. However, peri-operative beta-blockade does reduce non-fatal myocardial infarction on the expense of an increased cardiovascular mortality and an increased rate of non-fatal stroke.

Example 2: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation [59].

The conclusion of this Cochrane review focuses on the significant increased mortality associated with use of class 1a antiarrhythmics (odds ratio 2.39; 95% confidence interval (CI) 1.03 to 5.59) [59]. The data of this outcome in class 1a antiarrhythmics in this review [59] as well as in the included randomised trials [60-67] were analysed using the matrix error approach.

In step I, we assessed the risk of systematic error and the risk of random error for the chosen outcome of each study (Figure 6, Table 5). In step II, the design error should be evaluated by assessing multiple outcome measures. However, in this example we only consider the outcome 'all-cause mortality', since other outcomes were found to be not statistically significantly different [59]. Therefore, no figure of step II is shown. In step III,

	Level of evidence	Standard error
		All cause mortality
Byrne-Quinn [60]	1d	2.02
Hillestad [61]	1d	2.00
Karlson [62]	1d	1.42
Lloyd [63]	1d	1.55
PAFAC [64]	1b	0.78
Sodermark [65]	1d	0.73
SOPAT [66]	1b	1.51
Steinbeck [67]	1d	Z
Lafuente-Lafuente [59]	1c	0.43

Table 5: Ordering of evidence according to levels of evidence (systematic error), standard error (random error), and outcome measures (design error) in antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation (example 2).

Z: outcome with zero-events in both treatment arms which makes SE incalculable;
In this example the formulas for SE of $lnOR_{peto,I}$ for individual studies and SE of $lnOR_{peto}$ for meta-analysis were used.

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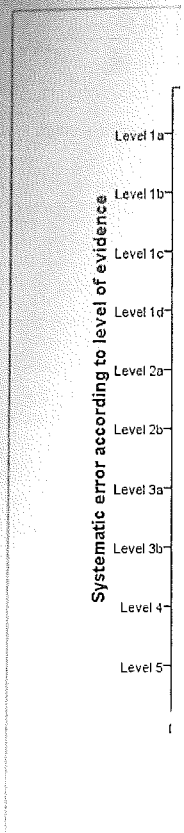

Figure 6: Mat
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we constructed the three-dimensional matrix (Figure 7). We did not elaborate on the matrix step IV in this example, since the available studies are not internally valid (high risks of both systematic and random error).

From Figure 7 it can be concluded at a glance that there is both substantial risk of systematic and random error involved in the evidence available so far considering mortality associated with class 1a antiarrhythmics. The best available level of evidence 1c study shows substantial risk of random error (0.43) and the best available level of evidence 1b study shows high risk of random error (0.78). So, the conclusion in the Cochrane review of a significant increased mortality is based on data with high risks for both systematic and random errors, and should therefore be considered unreliable.

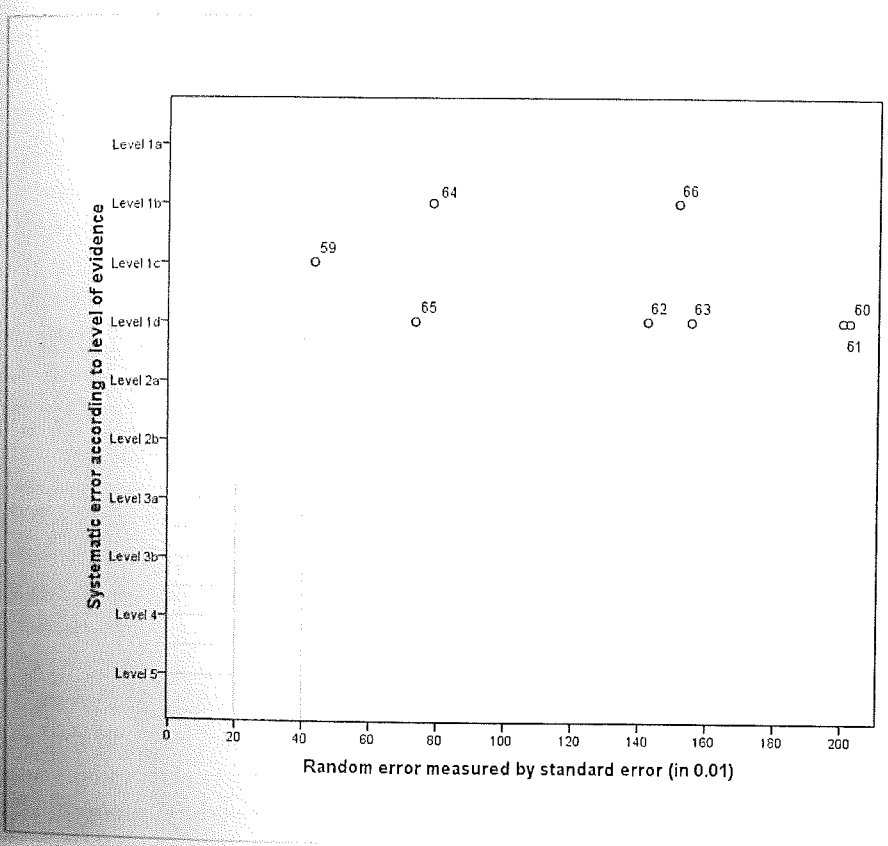

Figure 6: Matrix step I, ordering of evidence according to systematic error (in levels of evidence) and random error (measured by standard error) considering all-cause mortality in antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation (example 2).

Compare this figure with Figure 3: the studies in this figure are located on the right side of the figure (all SE > 0.40), in contrast with Figure 3 where the studies are concentrated on the upper left side of the figure (six studies with SE < 0.40).

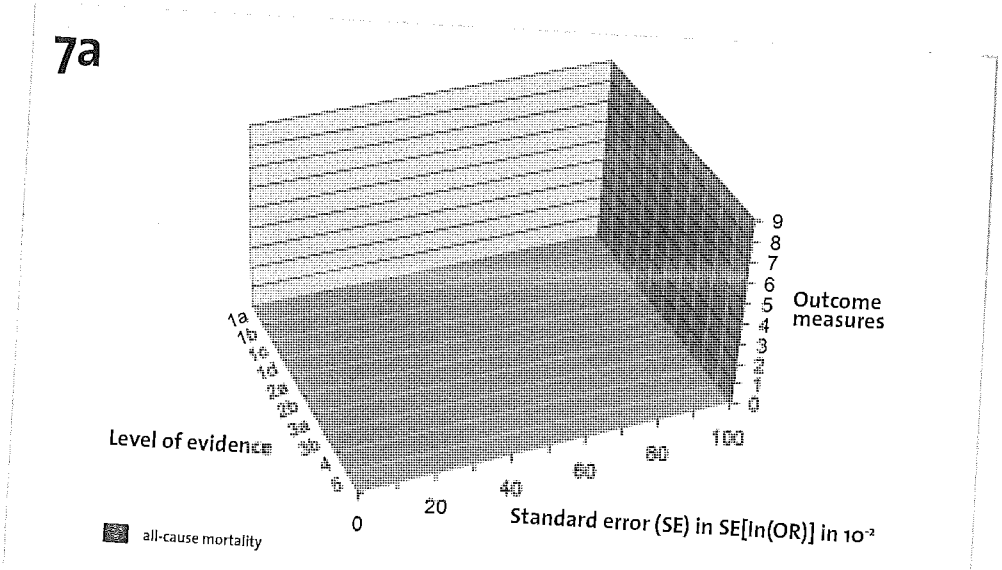

Figure 7a: Outcomes with benefit of antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.

Manhattan-like three-dimensional matrix building upon the risks of systematic error, random error, and design error. The evidence with the lowest systematic, random, and design error is represented by the tallest skyscrapers, located on 'the upper west side'.

A "quick guide' to the perception of the figure:
If you want to know what the evidence is for antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation to influence all-cause mortality: go to the red bars and read 1) Level of evidence (the risk of systematic error) and 2) standard error (the risk of random error).

Only the Cochrane review and the trials included in this systematic review were considered in this example. Data with risk of random error SE>1.0 were omitted from the figure. The SE of outcomes with zero events cannot be calculated.

From these 'benefit' and 'harm' Manhattan figures, one can see at a glance that there is no benefit at all and that 'the upper west side' is empty. Class 1a antiarrhythmics might increase mortality; however, since high risks for both systematic error and random error are present there is insufficient evidence for reliable conclusions.

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Figure 7b: Outcomes

DISCUSSION

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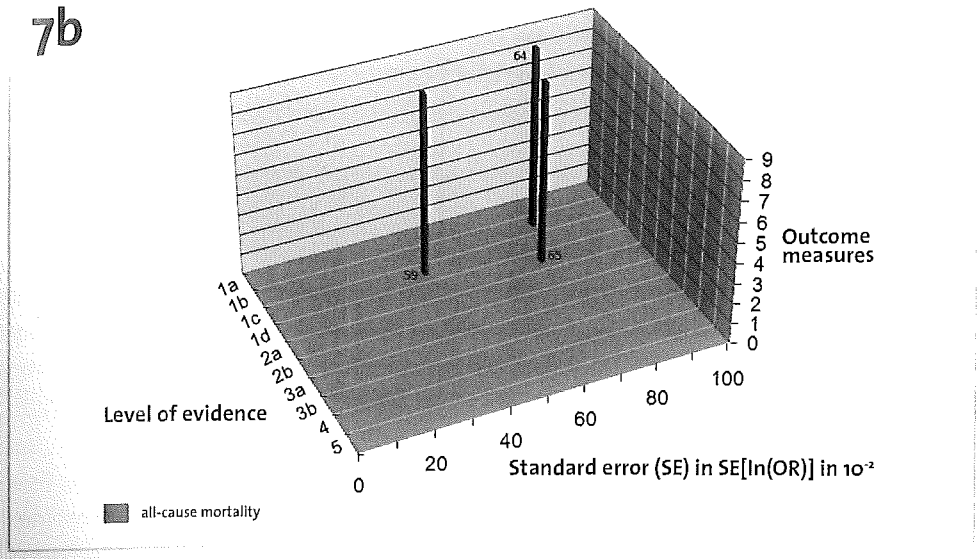

Figure 7b: Outcomes with harm of antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.

DISCUSSION

The aim of our matrix is to facilitate the overview of evidence in clinical intervention research. The matrix can serve as a tool to provide visual assessment of reliability of observations with respect to systematic error, random error (internal validity), and design error (external validity).

The matrix should not replace the thorough process of systematically reviewing evidence and profound evaluations of data, but could be integrated within these research activities as a tool for overviewing the results. Also, this matrix is not an absolute measure of the risks of errors. The position of studies in relation to each other is relative rather than absolute.

There is a lack of awareness of the importance of the 'play of chance' for the reliability of study findings. Ordering the standard errors of the studies might be a tool for ranking studies according to the level of random error. We have used natural logarithm (ln) transformations for calculating standard errors, although the logarithm with the base 10 may be used without producing different conclusions.

As an alternative, the Bayes factor can be considered [37,68]. The Bayes factor is a likelihood ratio comparing one hypothesis versus another, and, therefore, varies with the definition of the possible alternative hypotheses. The Bayes factor is a summary

measure that provides an alternative to the p-value for the ranking or the flagging of associations as 'significant' [69]. The Bayes factor:

$$\text{Bayes factor} = \frac{\text{Probability (Data, given the null hypothesis)}}{\text{Probability (Data, given the alternative hypothesis)}}$$

or simple approximations can be very difficult or even impossible to implement for the clinician, since a search for the maximum of the multidimensional posterior may be required for each association [69]. This also includes the asymptotic Bayes factor introduced by Wakefield [69]. In contrast to the Bayes factor, it is possible to calculate the standard error and when available it provides a tool for comparison of the risk of random error between studies of the same intervention.

The aim of minimising error risks according to the three dimensions actually combines the methodological efforts of falsifying any alternative hypothesis in the evaluation of an intervention. Thereby, the matrix concept visualises how far the scientific process has evolved to fulfil Poppers falsification criterion stating that researchers should primarily engage trying to falsify any relevant alternative hypothesis and not only the null hypothesis [5]. The minimisation of systematic errors and random errors, by providing ample room for the null hypothesis, as well as measuring important outcomes is the most audacious attack on any realistic alternative hypothesis. If an array of progressively qualified attacks fails to support the null hypothesis then we can reliably trust the intervention to be either beneficial or harmful.

The conclusion based on an assessment of the evidence using the matrix approach may be implemented into clinical practice or serve as an incentive for new research. The matrix facilitates the identification of lacunae in our knowledge and is likely to benefit the process of developing evidence-based guidelines.

Preference for the highest evidence

One has to be aware of the multiple forms of bias, potentially present in evidence below level 1 (Table 2). Several examples illustrate that large, apparently beneficial intervention effects from lower level evidence, even from randomized trials [54,56,70], may eventually be reversed to harmful effects when new high-quality evidence appears [50,71]. This is where the three dimensions of error are of central importance in providing a tool for reliability assessment.

Limitations

Apart from the three error dimensions influencing the reliability of data, other factors

play a role in incomparability and uncertainty of inferences. Many reports of studies appear incomplete, and the lack of details raises questions. Incomplete reporting limits interpretation, but more importantly, this reporting factor should be distinguished from the methodological quality of the trial [72].

Statements like CONSORT [73], PRISMA [74], and MOOSE [75] aim to improve and to maximize the amount and correctness of information to be retrieved from publications. These guidelines also create awareness among researchers about the most important issues to report so that the quality of future research may increase. By following reporting guidelines the yield of the research question is likely to be increased (phase 1 in Figure 1).

Standard error does not consider testing of multiple outcomes and multiple testing on accumulating data, which may also induce risks of random error due to multiplicity as well as correlations.

The division of all outcomes into 'primary' and 'secondary' outcome measures can be helpful as this division sets the standards for the evaluation of interventions. However, this division is artificial, and outcome measures, situated on the border of primary and secondary outcomes, exist. For example, one can argue that quality of life is a primary outcome rather than a secondary outcome. Further, there is also a quantitative aspect in the artificial division into primary and secondary outcomes. Small significant differences in primary outcome measures (e.g., bile duct injuries in patients undergoing cholecystectomy) may be found favouring one intervention, while large differences in secondary outcome measures (e.g., costs) may favour the comparator. Eventually, one may prefer the larger advantages in secondary outcomes to the smaller disadvantages in a primary outcome measure.

Another limitation in the outcome measure dimension is that often outcome measures are correlated and mostly this correlation is ignored. For example when mortality is an outcome measure and complications is another, which again counts deaths as complications, then there is a correlation between the two outcome measures. Authors usually carry out multiple univariate analyses ignoring correlations between outcome measures.

Step IV of the matrix includes the assessment of the size of the intervention effect, e.g., expressed in numbers-needed-to-treat to obtain benefit or to harm one patient with the intervention. This step is the last one since it is irrelevant to consider effect sizes and their directions if a study does not appear to be internally and externally valid.

Another aspect to consider is heterogeneity [76,77]. Statistical heterogeneity reflects the between trial variance of meta-analytic intervention effect estimates rather than

the play of chance [76]. Clinical heterogeneity, however, represents differences in populations, procedures, or interventions in daily practice. All these factors of clinical heterogeneity, together with concordance of in- and exclusion criteria should be considered whenever we want to implement results of available evidence. Assessment and consideration of heterogeneity or diversity, therefore, forms the final step before new evidence is implemented. Assessment of heterogeneity is not included in our matrix.

CONCLUSIONS

Assessment of risks of systematic error, random error, and design error are essential factors in evaluating evidence and drawing conclusions. We used the standard error in our matrix to rank studies according to their risk of random error. The risks of these error types were incorporated into a three dimensional matrix to create a schematic overview of the internal and external validity of the evidence, seen at a glance.

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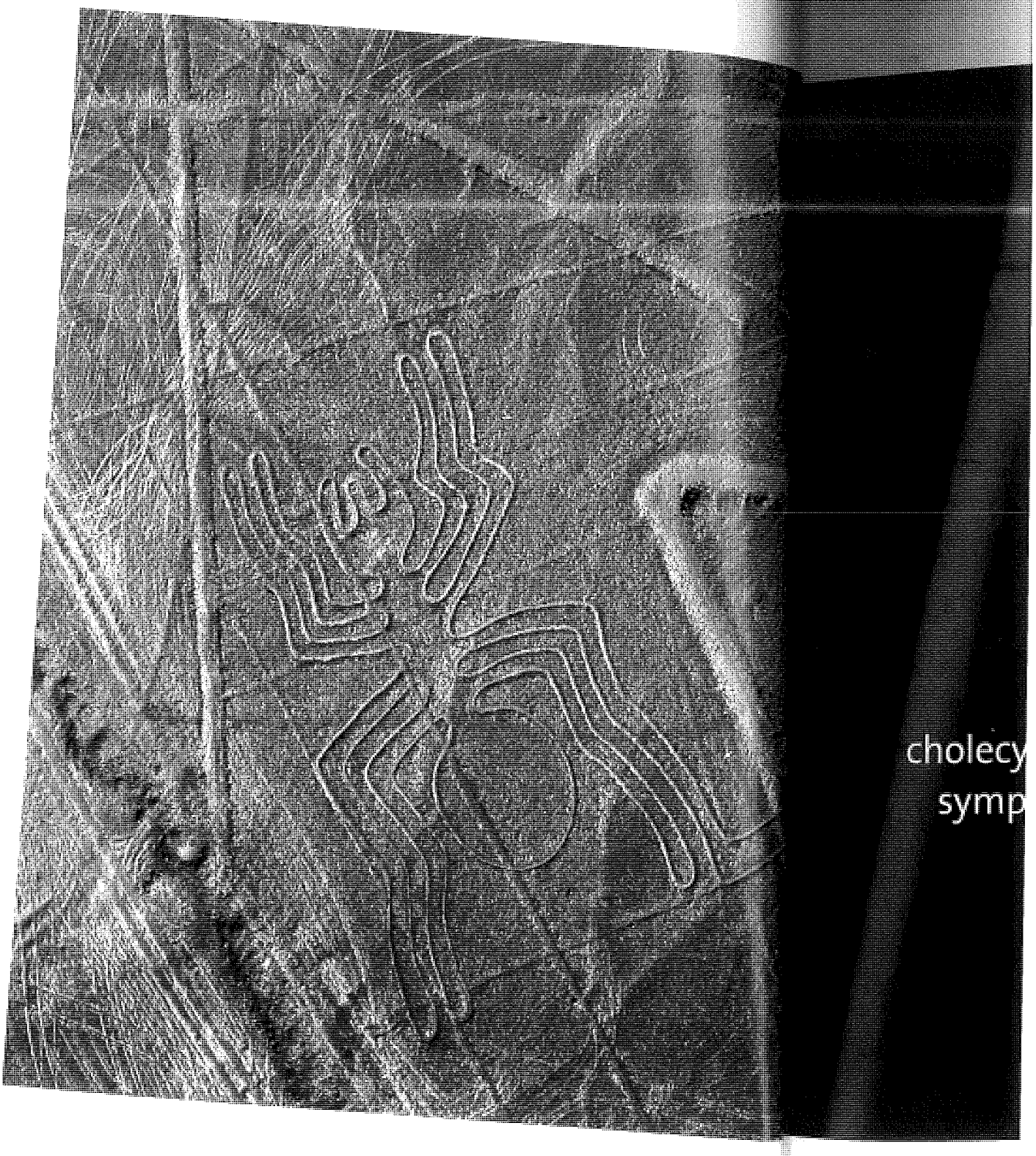

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Small-incision versus open cholecystectomy for patients with symptomatic cholecystolithiasis

F. Keus, J. A. F. de Jong, H. G. Gooszen, C. J. H. M. van Laarhoven

Cochrane Database Syst Rev 2006;Issue 4:CD004788

ABSTRACT

Background

Cholecystectomy is one of the most frequently performed operations. Open cholecystectomy has been the gold standard for over 100 years. Small-incision cholecystectomy is a less frequently used alternative.

Objectives

To compare the beneficial and harmful effects of small-incision versus open cholecystectomy for patients with symptomatic cholecystolithiasis.

Search strategy

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (6 April 2004), The Cochrane Library (Issue 1, 2004), MEDLINE (1966 to January 2004), EMBASE (1980 to January 2004), Web of Science (1988 to January 2004), and CINAHL (1982 to January 2004) for randomised trials.

Selection criteria

All published and unpublished randomised trials in patients with symptomatic cholecystolithiasis comparing any kind of small-incision or other kind of minimal incision cholecystectomy versus any kind of open cholecystectomy. No language limitations were applied.

Data collection and analysis

Two authors independently performed selection of trials and data extraction. The methodological quality of the generation of the allocation sequence, allocation concealment, blinding, and follow-up was evaluated to assess bias risk. Analyses were based on the intention-to-treat principle. Authors were requested additional information in case of missing data. Sensitivity and subgroup analyses were performed if appropriate.

Main results

Seven trials randomised 571 patients. Bias risk was high in the included trials. No mortality was reported. The total complication proportions are respectively 9.9% and 9.3% in the small-incision and open group, which is not significantly different (risk difference all trials, random-effects 0.00, 95% confidence interval (CI) -0.06 to 0.07). There are also no significant differences considering severe complications and bile duct injuries. However, small-incision cholecystectomy has a shorter hospital stay (weighted mean difference, random-effects -2.8 days (95% CI -4.9 to -0.6)) compared to open cholecystectomy.

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Authors' conclusions

Small-incision and open cholecystectomy seem to be equivalent regarding risks of complications, but the latter method is associated with a significantly longer hospital stay. The quicker recovery of small-incision cholecystectomy compared with open cholecystectomy confirms the existing preference of this technique over open cholecystectomy.

Only the abstract rather than the full text of the Cochrane systematic review is printed here due to space limitations. The full text may be accessed at the Cochrane Library (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD004788/frame.html). Instead, the sister publication in Alimentary, Pharmacology & Therapeutics summarizing the results of chapters 3, 4, and 5 is printed hereafter.

Systematic review: open, small-incision or laparoscopic cholecystectomy for symptomatic cholecystolithiasis

F. Keus, H. G. Gooszen, C. J. H. M. van Laarhoven

Aliment Pharmacol Ther 2009;29(4):359-378

(Chapters 3, 4, and 5 summarised)

ABSTRACT

Background
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ABSTRACT

Background
Laparoscopic cholecystectomy has become the method of choice for gallbladder removal, although evidence of superiority over open and small-incision cholecystectomy is lacking.

Aim
To compare the effects of open, small-incision, and laparoscopic cholecystectomy techniques for patients with symptomatic cholecystolithiasis.

Methods
We conducted updated searches until January 2007 in multiple databases. We assessed bias risk.

Results
Fifty-nine trials randomized 5556 patients. No significant differences in primary outcomes (mortality and complications) were found among all three techniques. Both minimal invasive techniques show advantages over open cholecystectomy in terms of convalescence. Small-incision cholecystectomy showed shorter operative time compared with laparoscopic cholecystectomy (random-effects, weighted mean difference, 16.4 min; 95% confidence interval, 8.9-23.8), but the two techniques did not differ regarding hospital stay and conversions.

Conclusions
No significant differences in mortality and complications were found among all three techniques. Laparoscopic cholecystectomy and small-incision cholecystectomy are preferred over open cholecystectomy for quicker convalescence. Laparoscopic cholecystectomy and small-incision cholecystectomy show no clear differences on patient outcomes.

INTRODUCTION

Gallstones are one of the major causes of morbidity in western society. It is estimated that the incidence of symptomatic cholecystolithiasis is up to 2.2 per thousand inhabitants [1,2] with an annual performance rate of cholecystectomies of more than 500 000 in the US [3-5]. Open cholecystectomy (OC) has been the gold standard for treatment of symptomatic gallstones since the 1880s [6]. Since the early 1970s, incisions were shortened, resulting in small-incision cholecystectomy (SIC). Morbidity and complications seemed to decline and patients recovered faster [7,8]. The first laparoscopic cholecystectomy (LC) was introduced in 1985 [9]. LC rapidly became the method of choice for removal of the gallbladder [4], although evidence of superiority over SIC and OC was lacking. This rising popularity was based on many arguments, including assumed advantages such as fewer complications and quicker post-operative recovery. LC seemed superior based on nonrandomized observations [5,10-13], but these comparisons may not provide an adequate assessment of intervention effects. However, conflicting data on clinical outcomes arose from randomized trials.

Despite several randomized trials assessing OC, SIC and LC, no systematic review with meta-analysis of these trials has been conducted. The objectives of our review were to evaluate the beneficial and harmful effects of the three different types of cholecystectomy for patients with symptomatic cholecystolithiasis.

METHODS

We conducted the review according to our peer-reviewed, published protocol [14] following the recommendations in the 'Cochrane Handbook for Systematic Reviews of Interventions' [15].

Criteria for considering trials

Only randomized trials were included comparing SIC vs. OC, LC vs. OC, or LC vs. SIC. Trials were included irrespectively of numbers of patients randomized, blinding, and language of the article. Quasi-randomized studies were excluded.

Participants in the trials were patients with one or more stones in the gallbladder confirmed by ultrasonography or other imaging technique and symptoms attributable to them, scheduled for cholecystectomy. Trials that included a small proportion of patients with acute cholecystitis in addition to patients with symptomatic cholecystolithiasis were included. Trials that only included patients with acute cholecystitis were excluded.

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Small-incision cholecystectomy was defined by an incision length of 8 cm or less, either vertical or transverse. The length of incision up to 8 cm was chosen arbitrarily as, in literature, most authors used this cut-off point between SIC and (conversion to) OC [16-19]. Any other open procedure with an incision length exceeding 8 cm was considered an OC.

Laparoscopic cholecystectomy included those procedures that started as a laparoscopic procedure. Any kind of LC was considered with creation of a pneumoperitoneum (by Veress needle or open introduction) or mechanical abdominal wall lift, irrespective of the number of trocars used.

The primary outcome measures were mortality, complication proportions, and relief of symptoms (pain relief). Secondary outcome measures were conversions, operative time, hospital stay, convalescence time, pulmonary function, pain scores, analgesic use, and health-related quality-of-life according to availability.

Search strategy

We updated the search of our published reviews up to January 2007. We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (8 February 2007), CENTRAL on The Cochrane Library (Issue 1, 2007), The National Library of Medicine (MEDLINE) (1966 - January 2007), The Intelligent Gateway to Biomedical & Pharmacological Information (EMBASE) (1980 - January 2007), ISI Web of Knowledge (Web of Science) (1988 - January 2007), and CINAHL (1982 - January 2007) for randomized trials (Table 1). Additional relevant trials were looked for by cross reference checking of identified randomized trials. All trial authors were requested for additional information lacking from their reports.

Methodological quality

Methodological quality, study design, and reporting quality have been recognized as criteria which can restrict bias in the comparisons of interventions. Inadequate methodological quality in randomized clinical trials carries the risk of overestimating intervention effects [20-22]. We assessed methodological quality of included trials using the following components: generation of the allocation sequence, allocation concealment, blinding, and follow-up. These four methodological components were scored adequate, unclear or inadequate /not performed according to Cochrane definitions [14,15]. Low-bias risk trials were defined by trials that scored adequate in three or more of the four above-mentioned methodological quality criteria. Pooled results including all trials were compared to pooled results from low-bias risk trials to assess the effect of methodological quality on the estimated intervention effect.

Database	Time span of search	Search of strategy	Hits	Titels selected
The Cochrane Hepato-Biliary Group Controlled Trials Register	8 February 2007	(cholecystectomy OR incision*) AND (gallstone* OR cholelithiasis OR (stones AND gallbladder))	911	68
Cochrane Database of Systematic Reviews in The Cochrane Library	Issue 1, 2007	cholecystectomy	73	0
Database of Abstracts of Reviews of Effects in The Cochrane Library	Issue 1, 2007	cholecystectomy	29	5
Cochrane Central Register of Controlled Trials in The Cochrane Library	Issue 1, 2007	cholecystectomy	1485	156
Health Technology Assessment Database in The Cochrane Library	Issue 1, 2007	cholecystectomy	14	4
NHS Economic Evaluation Database in The Cochrane Library	Issue 1, 2007	cholecystectomy	77	8
MEDLINE	1950 to January 2007	(((Gallbladder[Tiab] AND (Surgery[Tiab] OR Endoscopy[Tiab] OR Surgical[Tiab] OR Laparoscopy[Tiab])) OR Cholecystectomy[Tiab]) OR ((("Gallbladder"[MeSH] OR "Gallbladder Diseases"[MeSH]) AND ("Surgery"[MeSH] OR "surgery"[Subheading] OR "Endoscopy, Gastrointestinal"[MeSH] OR "Surgical Procedures, Operative"[MeSH] OR "Surgical Procedures, Minor"[MeSH] OR "Laparoscopy"[MeSH])) OR "Cholecystectomy"[MeSH])) AND (randomized controlled trial[PTYP] OR randomized controlled trials OR controlled clinical trial[PTYP] OR clinical trial[PTYP] OR clinical trials OR (clinical AND trial) OR random allocation OR random* OR double blind method OR single blind method OR (singl* OR doubl* OR trebl* OR tripl*) OR blind* OR mask* OR placebo* OR placebos OR research design OR comparative study OR evaluation studies OR follow up studies OR prospective studies OR control OR controlled OR prospectiv* OR volunteer*)	9246	371
EMBASE	1966 to January 2007	cholecystectomy	768	137
Web of Science	1988 to January 2007	TS=(cholecystectomy AND random*)	1546	157
CINAHL	1982 to January 2007	cholecystectomy	957	9
Total			15106	915 (620)

Table 1: Databases, used search strategies, and results of laparoscopic versus small-incision cholecystectomy.

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Hits	Titels selected
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incision cholecystectomy.

Extraction of data

Inclusion and exclusion criteria used in each trial were considered. We extracted: number of randomized patients, number (and reasons) of patients not randomized, number of patients excluded after randomization, number of drop-outs, information on intention-to-treat analysis, sample size calculation, single- or multi-centre design, primary and secondary outcome measures, antibiotic prophylaxis, surgical experience, and intra-operative cholangiography.

General descriptive data (like gender, age, body mass index (BMI), and American Society of Anaesthesiologists (ASA) classification) are supposed to be equally divided due to randomization [23]. Trials were assessed for imbalance in general descriptive data. Outcome data were extracted according to availability.

For reasons of the wide range of the types of complications described, all complications were categorized into four subcategories: intra-operative, minor, severe, or bile duct injury. Furthermore, total complication proportions were calculated. As bile duct injuries are considered the most important complication in cholecystectomy, these were registered separately from all the other complications and hence not counted as severe or minor adverse event. Intra-operative complications may reflect immediate differences in techniques; therefore, the intra-operative complications (excluding all bile duct injuries) were categorized separately from other complications. All other complications were categorized into minor and severe complications. Complications which were possibly life-threatening (e.g. cardiac, pulmonary, and bleeding) and complications with a major impact on postoperative quality of life or recovery time (e.g. re-operations) were categorized as severe complications. All other complications with mild consequences were categorized as minor complications.

Statistical analysis

Exploration of the data showed that for many binary data, the outcome was rare or zero in one or both arms. In Review Manager (http://www.cochrane.org), odds ratios and relative risks (RRs) are not estimable in trials with zero events in both arms; therefore, risk differences have been used in our Cochrane review. However, alternative software allows for calculating RRs including the zero event trials by using continuity corrections. For reasons of consistency of effect, ease of interpretation, and mathematical properties, binary outcomes were expressed in RRs using Trial Sequential Analysis software (Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen, Denmark) [24-27].

Continuous data were presented in weighted mean differences (WMD). For the analysis, mean values with their corresponding standard deviations are needed to calculate WMD with 95% confidence intervals (CI).

Funnel plots were used for visual assessment of the presence of publication bias and whether treatment estimates were associated with study size.

Depending on the presence of heterogeneity, the results of the random- [28] or fixed-effect model [29] were presented. Heterogeneity was calculated by the Cochran's Q test and quantified by measuring I^2 [15]. Arbitrarily, an I^2 of 25% distinguished between using a fixed- or random-effects model.

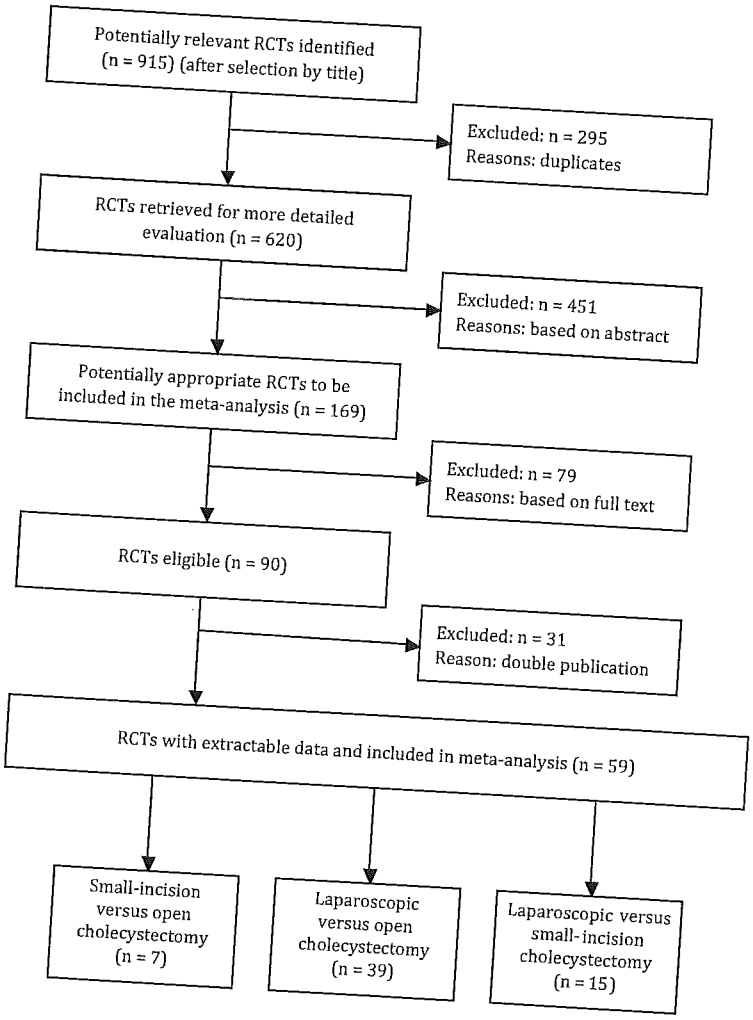

Figure 1: QUOROM statement flow diagram summarizing the numbers of trials in each phase of the review and meta-analysis evaluating techniques of cholecystectomy for symptomatic cholecystolithiasis.

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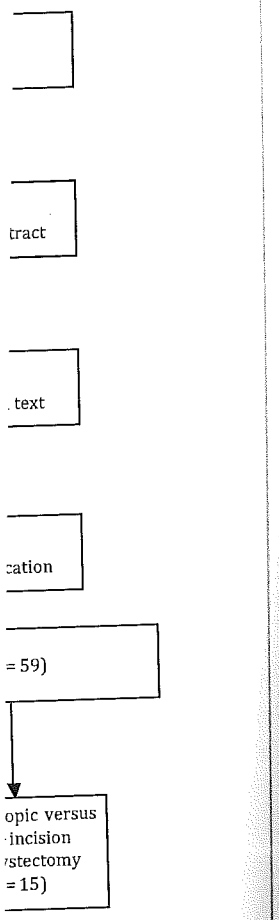

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Chapter 3, 4, 5

Subgroup and sensitivity analysis

Two types of subgroup analyses were performed. First, subgroup analyses according to each of the quality criteria domains were performed to compare the effects of the interventions according to the methodological quality of the trials (adequate compared to unclear / inadequate). Second, high- and low-bias risk trial subgroup analyses were conducted according to classification of the trials (defined by three or more adequate quality domains). Sensitivity analyses were performed for continuous outcomes imputing data for missing values.

RESULTS

Altogether, the search resulted in 15 106 hits. In each step of selection, we included the publication in case of any doubt. After selections by titles (915) and correction for duplicates, 620 publications remained. The abstracts of these 620 publications were reviewed independently by two authors and differences were discussed. A total of 451 publications could be rejected based on their abstract. Eventually, 169 publications were selected for further evaluation from which a total of 79 were excluded (Figure 1). A total of 59 trials were described in 90 publications [30-32].

Two trials were only described in short [33,34]. As no language restriction was used, four publications were translated [35-38]. Double publications of trial results by the same research group were considered one trial [39-44]. After contacting individual trialists, additional data and information were obtained from 10 out of 59 trials.

Patient characteristics and trial designs

All included trials used similar inclusion criteria. The extensiveness in which exclusion criteria were described varied, but nearly all trials excluded patients with acute cholecystitis. We did not find any imbalance in baseline data on age, gender, BMI and ASA classification.

One trial used a three-arm design [17]. Another trial used a five-arm design comparing LC in one arm versus OC in four arms with variable application of medication treatment to reduce post-operative paralytic ileus. We summarized all OC patients in one group, resulting in a ratio of one to four of included patients in both groups [45]. The trial by Lausten included two groups: patients with postnecrotic liver cirrhosis and patients with chronic hepatitis (both groups ASA classifications III and IV). Both groups were randomized separately. For data management reasons, we listed both groups as separate trials [46,47]. All other trials used a two-arm parallel-group design.

7

Trial sequential analyses of meta-analyses of complications in laparoscopic vs. small-incision cholecystectomy: more randomized patients are needed

F. Keus, J. Wetterslev, C. Gluud, H. G. Gooszen, C. J. H. M. van Laarhoven

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ABSTRACT

Objective

Conclusions based on meta-analyses of randomized trials carry a status of "truth". Methodological components may identify trials with systematic errors ("bias"). Trial sequential analysis (TSA) evaluates random errors in meta-analysis. We analyzed meta-analyses on laparoscopic vs. small-incision cholecystectomy regarding different outcome measures for the occurrence of type I errors.

Study Design and Setting

Using TSA, we calculated the required information size (IS) and the trial sequential monitoring boundaries regarding complications in our Cochrane review with meta-analyses of cholecystectomy. For each outcome, we calculated a low risk of bias heterogeneity-adjusted IS. As a sensitivity analysis, we calculated an a priori heterogeneity-adjusted IS.

Results

According to the trial sequential analyses based on a low risk of bias heterogeneity-adjusted IS definitive evidence may be reached by conducting one more randomized trial. Information may be required on 582 and 119 additional randomized patients to evaluate the effect on severe complications and serious adverse events (SAEs), respectively.

Conclusion

Our results provide incentives to conduct a new trial with a low risk of bias focusing on a new composite outcome measure of SAEs to obtain conclusive evidence on which operative method to recommend.

INTRODUCTION

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INTRODUCTION

The number of Cochrane reviews and the availability of The Cochrane Library worldwide have increased during the last decade [1]. The development and application of evidence-based guidelines, usually based on the highest level of evidence, that is, systematic reviews of randomized trials with low risk of bias, have also increased [2].

The conclusions based on such reviews with meta-analyses may carry a status of "truth", and scepticism tends to be sparse. However, there is a high probability that differences between treatments are found because of random errors ("the play of chance") [3,4], systematic errors ("bias") [5-8], and design errors ("wrong design to answer the question posed" or "wrong context", e.g., lack of sufficient education in one of the interventions) [9]. Potentially spurious results may arise because of random errors (type I and II errors), when a limited number of trials and patients are included and with frequent updating of the cumulative meta-analysis [3,4].

In the planning of a randomized trial, the sample-size calculation provides an insight into the ability to detect an intervention effect with sufficient power. The sample size is calculated to detect a prespecified intervention effect with a risk of type I (α) and type II (β) error [10]. It is inappropriate to make conclusions based on small differences between treatments from a randomized trial with only few patients included. Likewise, it may be inappropriate to draw conclusions from a meta-analysis when information is sparse [4]. Without evaluating how much information is needed and how much we have at hand, we may not be able to reliably assess the results. Consequently, we might well draw inappropriate conclusions because of random errors in a cumulative meta-analysis with too little information.

We have conducted trial sequential analysis (TSA), based on the calculation of the heterogeneity-adjusted required information size (IS) and the analysis of the cumulative z-curve [4,11-15]. In a cumulative meta-analysis, the pooled intervention effect estimate is updated whenever a new trial is added according to the chronological sequence of publishing. The cumulated z-values can be calculated and plotted against the new cumulated IS obtained [4,11-15]. Further, trial sequential monitoring boundaries (TSMBs) can be constructed and the relation of the z-curves to the boundaries may determine whether firm evidence is established or not in the meta-analysis [4,11-15].

We conducted a Cochrane Hepato-Biliary Group review with meta-analyses comparing laparoscopic vs. small-incision cholecystectomy for patients with symptomatic cholecystolithiasis [16]. This review is in the process of being updated, and 15 trials with a total of 2,582 randomized patients were included [17]. The question is whether the

required IS has been reached to detect or reject a worthwhile and realistic intervention effect or whether possible differences reflect spurious P < 0.05 values (type I error).

Aim

The aim of this study was to calculate the required IS and the TSMB for the meta-analyses of our Cochrane review on laparoscopic and small-incision cholecystectomy for patients with symptomatic cholecystolithiasis.

METHODS

Data

There are many kinds of complications in cholecystectomy; they were categorized into four subcategories in our Cochrane review [16]: intraoperative, minor, severe, and bile duct injury. Further, total complication proportions were calculated. Bile duct injuries were registered separately from the other complications and hence not counted as intraoperative, severe, or minor adverse event. Likewise, the intraoperative complications, excluding bile duct injuries, were categorized separately from the minor and the severe complications. As the number of complications was reported and not the number of patients with complications, patients may occasionally have been double counted [16].

Intraoperative, minor, severe, and bile duct injury complications have been considered to be independent outcome measures. The total complication category, however, summarizes all complications and is thus not independent of the other outcome categories. We considered total complications the most important outcome measure in our systematic review. However, total complications also include complications, which can hardly be considered critical for decision making according to the Grade categorization of outcomes [9,18-20]. Therefore, it seems more sensible to compile all serious adverse events, considered critical for decision making, into a single composite outcome measure called "serious adverse events" (SAE). SAE includes mortality, bile duct injuries, severe complications, and clinically important intraoperative complications.

From a statistical point of view, analyses of multiple outcome measures require P-value adjustment, which is difficult when outcomes are not strictly independent. So despite the fact that all the outcomes defined may be of interest, we chose to analyze only the most important ones to reduce inflation of type I error by multiplicity of testing. Therefore, we analyzed mortality, the four complication subcategories, and total complications. Additionally, a composite outcome measure of SAE was generated and evaluated post hoc as a hypothesis-generating analysis.

Zero-event trials

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Zero-event trials

Several trials included in our review had zero events in one or both groups of surgical intervention. In a previous study, we evaluated the impact of different meta-analytical statistical methods on the conclusions of our review depending on the handling of the zero-event problem [21]. Based on this study and recommendations from the literature, we decided to use an empirical continuity correction of 0.01 in zero-event trials for the present analyses [16,21-24].

Bias protection

As randomized clinical trials with a high risk of bias may overestimate intervention effects [5,8,25], results of randomized clinical trials with a low risk of bias are considered more valid. Therefore, the risk of bias should be assessed based on the adequacy of the generation of the allocation sequence, allocation concealment, blinding, and follow-up [26]. In our Cochrane review, trials that were considered adequate regarding at least three of the four above-mentioned bias protection criteria were considered as low risk of bias [16].

Trial sequential analysis

Repeated testing on accumulating data may cause random errors [27]. Also, small trials may indicate significant findings which are in fact because of random errors. Such results are often overruled when results from adequately powered trials emerge [28,29]. TSA uses TSMB in a meta-analysis adopted from discrete sequential boundaries in a single trial to evaluate the amount of evidence actually reached [4,11-14]. TSA prevents premature declaration of superiority of an intervention that is misled by a random low P-value because of repeated testing in a cumulative meta-analysis. Apart from assessment of the presence of random error, TSA offers additional advantages such as reestimation of sample size, provides incentives for the conduct of new high-quality trials, and may stop trials if the intervention benefits are remote or nonexistent, either when the IS has been reached or when the intervention effect is dramatic and no more trials are needed [4,11-15]. The required IS may be calculated like the sample size of an adequately powered trial to detect a prespecified intervention effect with a risk of a type I (α) and a type II (β) error [4,11-15]. The desired IS in a meta-analysis may then be this sample size adjusted for the heterogeneity among the included trials in the meta-analysis [4,11-15].

For the calculation of the required IS, four components have to be specified: the risk of a type I error (α), the risk of a type II error (β), a control event rate (CER), and a relative risk reduction (RRR). Usually, α is set at 0.05, and the power ($1 - \beta$) is set at 0.80.

IS calculation based on a priori and low-bias intervention effects

The clinical importance of an a priori selected RRR will depend on the specific research question. Randomized trials with a high risk of bias may overestimate intervention effects compared with trials with a low risk of bias [5-8]. Therefore, it may be more valid to base the required IS calculation on the intervention effect estimated by the trials with a low risk of bias [4,11-15].

However, estimated intervention effects of trials with a low risk of bias may be smaller or larger than what is considered relevant from a clinical point of view. It is also possible that, by chance, a very large effect is measured in trials, despite a low risk of bias which may lead to an early false rejection of the null hypothesis. Evidence of a possible smaller effect may still be present legitimizing the conduct of new larger trials. Therefore, it seems useful to calculate the required IS based on both an a priori anticipated intervention effect and an intervention effect based on the estimate from the trials with a low risk of bias [4,11-15].

Heterogeneity

It is assumed in meta-analyses that participants involved in the different trials show similar intervention effects. However, heterogeneity may be present. As heterogeneity may influence the choice of a fixed-effect or a random-effects model in a meta-analysis, heterogeneity may influence the calculated required IS [4]. Therefore, heterogeneity ought to adjust IS in TSA calculations [4,11-15]. An increase in heterogeneity consequently results in a larger required IS before firm evidence can be obtained. Both the a priori and the low risk of bias IS should be heterogeneity-adjusted.

Statistical analysis

TSA calculations were performed considering the outcome measure of all complication categories. Relations between the cumulated z-curve determined by the random-effects model, the traditional criterion $z = 1.96$, the TSMB, and the required IS were analyzed. Two types of required IS calculations were used.

The a priori heterogeneity-adjusted IS (APHIS) calculation uses imputed values of CER and RRR based on clinical considerations. Before the analyses, consensus was reached among the authors that incidences in the small-incision group were taken as CER in all APHIS analyses and an arbitrary RRR of 20% was considered clinically relevant.

The low-bias risk heterogeneity-adjusted IS (LBHIS) uses values of CER and RRR estimated from the trials with a low risk of bias [4,11-14].

The findings of the well-conducted trials with a low risk of bias may be considered more

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RESULTS

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Mortality
Intra-operative complications
Minor complications
Severe complications
Bile duct injuries
Total complications
Composite outcome measure: 'serious adverse events'

Table 1: Number of events, even trials with zero events of eval

realistic compared with an a priori anticipated intervention effect. Therefore, the LBHIS calculations were conducted as primary analysis, and the APHIS calculations were conducted as sensitivity analysis.

"Firm evidence" is defined by a cumulative z-curve crossing the calculated IS needed or alternatively crossing the TSMB before the calculated IS needed has been reached. "Spurious results" are defined by a cumulative z-curve crossing the traditional z = -1.96 or z = 1.96 boundary but not the TSMB. Such results may represent random error as a result of repetitive testing on accumulating data (nominal type I error).

The analyses were performed using the TSA program (developed by The Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark). The results of using this program have been described in a number of meta-analyses [4,11-15].

RESULTS

A total of 15 randomized trials were included. A total of 2,582 patients were randomized to laparoscopic vs. small-incision cholecystectomy, with 1,291 in each group [16]. The event proportions in the laparoscopic group, the small-incision group, and the total group of patients, the number of participants, the number of trials with data, and the number of zero-event trials are listed in Table 1. Detailed data of each trial are listed in Table 2.

	LC	SIC	Total (LC + SIC)	Number of participants	Number of trials with data	Number of zero-event trials
Mortality	1 (0.1%)	1 (0.1%)	2 (0.1%)	1952	7	5
Intra-operative complications	153 (12.0%)	88 (6.9%)	241 (9.4%)	2560	14	10
Minor complications	98 (7.7%)	114 (8.9%)	212 (8.3%)	2560	14	3
Severe complications	48 (3.8%)	50 (3.9%)	98 (3.8%)	2560	14	4
Bile duct injuries	15 (1.2%)	22 (1.7%)	37 (1.4%)	2560	14	5
Total complications	314 (24.5%)	274 (21.4%)	588 (23.0%)	2560	14	2
Composite outcome measure: 'serious adverse events'	95 (7.4%)	100 (7.8%)	195 (7.6%)	2560	14	3

Table 1: Number of events, event rate (in brackets), total number of participants, number of trials with data, and the number of trials with zero events of evaluated binary outcome measures in laparoscopic (LC) and small-incision cholecystectomy (SIC).

Mortality

We found no statistically significant difference in mortality between laparoscopic and small-incision cholecystectomy. The LBHIS required reaches infinity and is incalculable (Table 3).

In a sensitivity analysis the APHIS required for detecting a significant difference in mortality is at least 86,000 patients (based on a 20% RRR and 0.08% CER).

Intraoperative complications

We found strong evidence for a statistically significant difference in intraoperative complications favoring small-incision cholecystectomy. The LBHIS required is 229 patients. The z-curve in the LBHIS calculation initially does not cross any boundary. However, the z- curve unexpectedly crosses the TSMB and the traditional z = -1.96 (P = 0.05) after having passed the LBHIS required. It is especially one trial that forces the z-curve to cross the TSMB [30]. This trial included gallbladder perforations as complications [30].

	Bias risk	Number of participants		Complications									
				intra-operative		minor		severe		bile duct injuries		total	
		LC	SIC	LC	SIC	LC	SIC	LC	SIC	LC	SIC	LC	SIC
Barkun 1992	High	37	25	0	0	0	1	1	0	0	1	1	2
Kunz 1992	High	50	50	0	0	0	0	2	1	0	1	2	2
Coelho 1993	High	15	15	0	0	0	1	0	0	0	0	0	1
Tate 1993	High	11	11	na	na	na	na	na	na	na	na	na	Na
McMahon 1994	High	151	148	0	0	19	19	4	12	4	3	27	34
McGinn 1995	High	155	155	0	0	5	2	8	0	1	2	14	4
Majeed 1996	Low	100	100	1	0	8	12	3	2	1	0	13	14
Bruce 1999	High	11	11	0	0	0	0	0	0	0	0	0	0
Ros 2001	Low	362	362	148	85	39	36	18	31	6	7	211	159
Srivastava 2001	High	59	40	0	1	0	11	0	0	1	5	1	17
Grande 2002	High	18	22	0	0	0	0	0	0	0	0	0	0
Secco 2002	High	86	86	0	0	16	14	4	1	0	0	20	15
Harju 2006	High	72	85	0	0	0	6	0	1	1	0	1	7
Keus 2006	Low	120	137	4	2	10	10	6	1	1	3	21	16
Vagenas 2006	High	44	44	0	0	1	2	2	1	0	0	3	3
Total		1291	1291	153	88	98	114	48	50	15	22	314	274

Table 2: Overview of the bias risk, the numbers of participants, and the numbers of complications of the included randomized trials in the Cochrane review with meta-analysis on laparoscopic (LC) versus small-incision cholecystectomy (SIC).

na: not available. High risk of bias = the trial is considered unclear or inadequate regarding two or more of the following four design components: generation of the allocation sequence, allocation concealment, blinding, follow-up. Low risk of bias = the trial is considered unclear or inadequate regarding one or none of the following four design components: generation of the allocation sequence, allocation concealment, blinding, follow-up.

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Intra-operative complications	APHIS
	LBHIS
Minor complications	APHIS
	LBHIS
Severe complications	APHIS
	LBHIS
Bile duct injuries	APHIS
	LBHIS
Total complications	APHIS
	LBHIS
Composite outcome measure: 'serious adverse events'	APHIS
	LBHIS

Table 3: Trial sequential ar heterogeneity adjusted inforn

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ct injuries		total	
	SIC	LC	SIC
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	1	2	2
	0	0	1
	na	na	Na
	3	27	34
	2	14	4
	0	13	14
	0	0	0
	7	211	159
	5	1	17
	0	0	0
	0	20	15
	0	1	7
	3	21	16
	0	3	3
	22	314	274

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In sensitivity analysis excluding intraoperative gallbladder perforations, there is a lack of evidence for a statistically significant difference in intraoperative complications (data not shown). The outlying result of this one trial explains the boundary crossing after having passed the LBHIS required.

In a sensitivity analysis, the APHIS required is 9,602 patients (based on a 20% RRR and 6.9% CER). The z-curve in the APHIS calculation crosses the TSMB curve after only 18% of the required IS (Figure 1).

Minor complications

We found no statistically significant difference in minor complications between the two operation methods. The z-curve fluctuates around zero not even approaching z = -1.96 (P = 0.05). The LBHIS cannot be calculated. The meta-analysis is underpowered to detect or reject an intervention effect suggested by the trials with a low risk of bias.

	APHIS or LBHIS based calculation	relative risk reduction (RRR)	control event rate (CER)	calculated IS needed	cumulative IS reached so far (%) *	cumulative z-curve crosses: traditional boundaries (p=0.05)	cumulative z-curve crosses: calculated TSMB	spurious significant difference may be present	firm evidence reached	how many additional participants may be needed
Mortality	APHIS	20%	0.08%	86000	2%	No	No	No	No	84048
	LBHIS	-	-	Infinity	-	No	No	No	No	Infinity
Intra-operative complications	APHIS	20%	6.9%	9602	27%	Yes	Yes	No	Yes	0 [‡]
	LBHIS	-75%	23%	229	1118%	No	No	No	No	0
Minor complications	APHIS	20%	8.9%	7302	35%	No	No	No	No	4742
	LBHIS	-0.8%	9.9%	Infinity	-	No	No	No	No	Infinity
Severe complications	APHIS	20%	3.9%	17478	15%	Yes	No	Yes	No	14918
	LBHIS	-37%	8.0%	3142	81%	Yes	No	Yes	No	582
Bile duct injuries	APHIS	20%	1.7%	40918	6%	No	No	No	No	38358
	LBHIS	26%	2.0%	19964	13%	No	No	No	No	17404
Total complications	APHIS	20%	21%	5354	48%	No	No	No	No	2794
	LBHIS	-32%	39%	1016	252%	No	No	No	Yes	0
Composite outcome measure: 'serious adverse events'	APHIS	20%	7.8%	11764	22%	No	No	No	No	9204
	LBHIS	-32%	16%	2679	96%	No	No	No	No	119

Table 3: Trial sequential analysis of a priori heterogeneity adjusted information size (APHIS) and low risk of bias based heterogeneity adjusted information size (LBHIS) on different binary outcome measures in laparoscopic (LC) and small-incision cholecystectomy (SIC).

*APHIS: a priori heterogeneity adjusted information size; LBHIS: low risk of bias based heterogeneity adjusted information size; IS: information size; RRR: relative risk reduction used for the IS calculation; CER: control event rate; TSMB: trial sequential monitoring boundary. * A total of 7 randomised trials including 1952 patients report mortality. A total of 14 randomised trials including 2560 patients report complications. [‡] Although the calculated IS needed (9602 participants) has not been reached yet (2560 participants so far), no more additional participants are needed since the cumulative z-curve crosses the TSMB.*

In a sensitivity analysis, the APHIS required is 7,302 patients and concurs with the LBHIS analysis.

Severe complications

We found a lack of firm evidence for a statistically significant difference in severe complications between the two operation methods. However, the z-curve crosses the traditional z = -1.96 boundary in the LBHIS analyses, whereas the z-curve does not cross the $TSMB_{LBHIS}$ (Figure 2). The LBHIS required is 3,142 patients (based on a 36.7% RRR and 8.0% CER). The conclusion is that the proportion of severe complications may or may not be different between the two operation methods. The meta-analysis is underpowered to detect or reject an intervention effect suggested by the trials with a low risk of bias.

In a sensitivity analysis, APHIS calculations are similar. The z-curve crosses the traditional z = -1.96 boundary, whereas the z-curve does not cross the $TSMB_{LBHIS}$. The APHIS required is 17,478 patients (based on a 20% RRR and 3.9% CER).

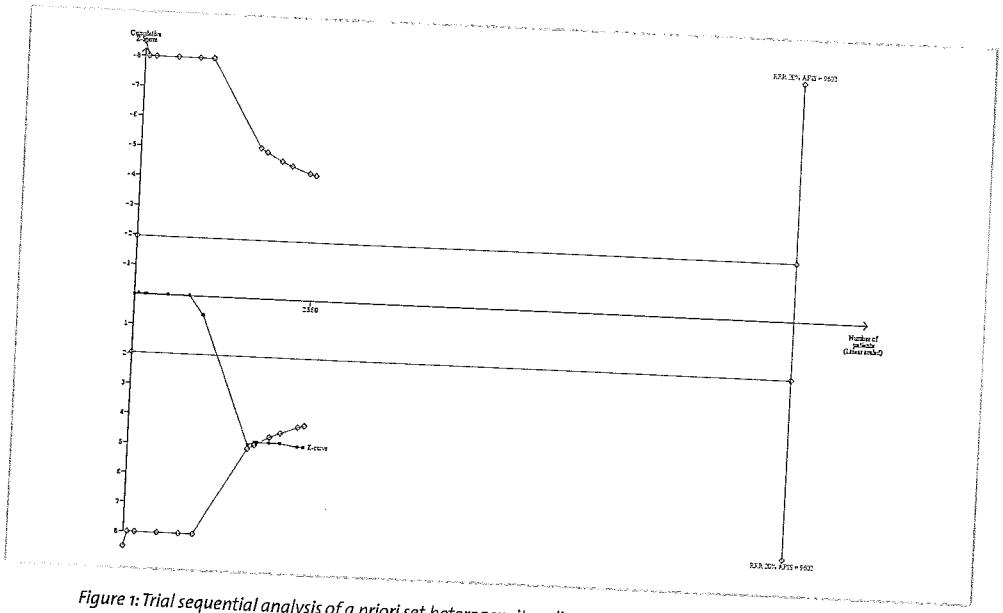

Figure 1: Trial sequential analysis of a priori set heterogeneity adjusted information size (APHIS) on difference in intra-operative complications between laparoscopic and small-incision cholecystectomy.

The z-value is plotted vertically. The numbers of patients are plotted horizontally. The vertical red line represents the calculated information size needed. The horizontal lines at z=-1.96 and z=1.96 indicate the traditional two-sided p = 0.05. The symmetrical red curves represent the calculated trial sequential monitoring boundaries. The blue line represents the cumulative z-value, with each consecutive trial marked by a filled circle. Firm evidence has been reached when the cumulative z-curve crosses the calculated boundaries before the calculated information size. Spurious significant differences between treatments are found when the cumulative z-curve crosses the traditional z=-1.96 or z=1.96, but not the calculated trial sequential monitoring boundaries. APHIS = 9,602 patients; meta-analysis has reached only 27% of this figure; relative risk reduction 20%; control event rate 6.9%. The Ros trial dominates the course of the z-curve [30].

Bile duct injuries

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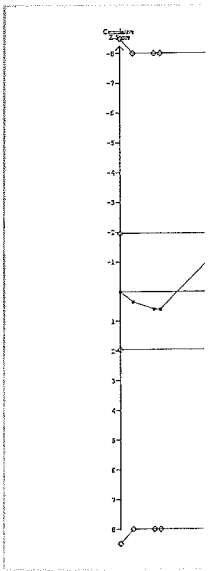

*Figure 2: Trial seq
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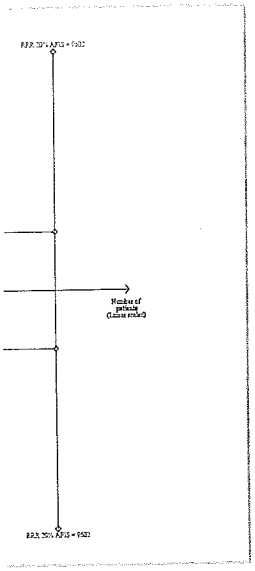

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Bile duct injuries

We found no statistically significant difference in bile duct injuries between the two operation methods. The z-curve does not even approach the traditional boundary. The LBHIS required is 19,964 patients. The meta-analysis is underpowered to detect or reject an intervention effect suggested by the trials with a low risk of bias.

In the APHIS, sensitivity analysis findings concur and 40,918 patients are required (suggested by a prespecified 20% RRR and a CER of 1.7%).

Total complications

We found no statistically significant difference in total complications between the two operation methods. In the LBHIS calculation, only 1,016 patients are required. According to the LBHIS, the meta-analysis appears to be overpowered and is able to reject an intervention effect of 31.7% RRR with a CER of 39.1% suggested by the trials with a low risk of bias. In the LBHIS analysis, the z-curve does not cross the traditional boundary of P = 0.05.

In a sensitivity analysis, the APHIS required is 5,354 patients (based on a 20% RRR and 21.4% CER), which suggests that the meta-analysis is underpowered to detect or reject an intervention effect (Figure 3).

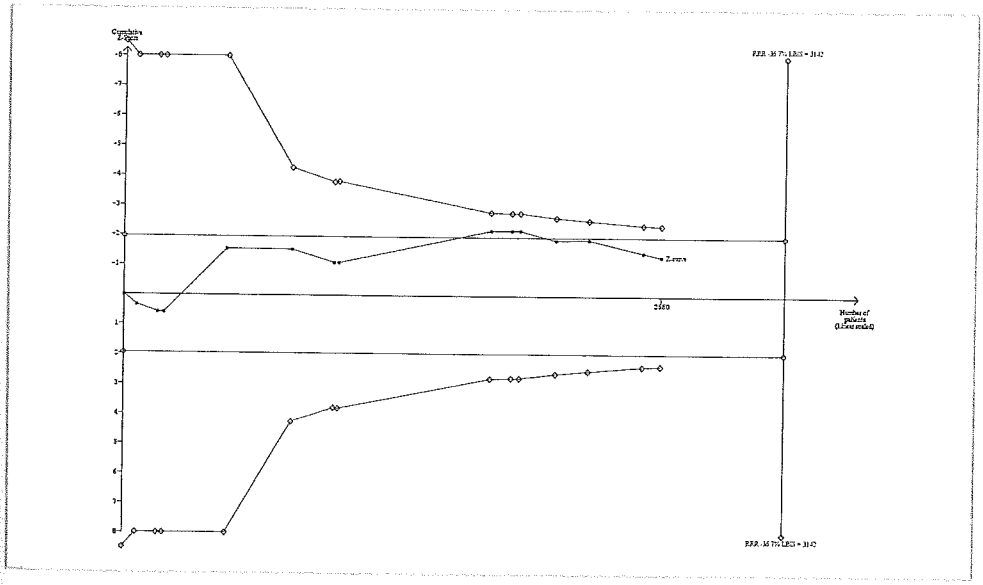

Figure 2: Trial sequential analysis of low risk of bias based heterogeneity adjusted information size (LBHIS) on difference in severe complications between laparoscopic and small-incision cholecystectomy.

LBHIS = 3142 patients; meta-analysis at 81%; relative risk reduction -36.7%; control event rate 7.96%.

Composite outcome measure: SAE

All serious complications (including mortality, bile duct injuries, severe complications, and severe intraoperative complications) were added into a composite outcome measure of SAE. We found no significant difference in SAE between the two operation methods (Figure 4). The z-curve does not cross the traditional boundary, but it fluctuates around zero. The LBHIS required is 2,679 patients. Only 119 more patients are needed to reject or detect an intervention effect of 31.5% RRR (with a CER of 15.7%) as suggested by the trials with a low risk of bias.

In a sensitivity analysis, the APHIS required is 11,764 patients (based on a 20% RRR and 7.8% CER), the z-curve does not cross z = -1.96, and the meta-analysis is underpowered to reject or detect an intervention effect of this magnitude. The APHIS analysis suggests that many more patients are needed to detect or reject the 20% RRR compared with the LBHIS analysis.

DISCUSSION

We have reanalyzed our meta-analysis data on complications associated with laparoscopic and small-incision cholecystectomy for patients with symptomatic cholecystolithiasis and calculated the required IS using the TSA program [16,17]. We find that firm evidence has been reached considering intraoperative complications and total complications by the LBHIS TSA analyses, favoring small-incision over laparoscopic cholecystectomy. However, the results are dominated by data from one of the trials [30], and analyses excluding intraoperative gallbladder perforations show no significant differences between the two operation techniques. Sensitivity APHIS TSA analyses show that definitive evidence has not been reached. Furthermore, we observe that there is no sufficient information as yet to reliably reject or accept potential differences in other complications between the two operative interventions.

Potentially spurious (random error) results favoring the laparoscopic technique were obtained while evaluating severe complications (Figure 2) [16]. Meta-analyses of severe complications and the composite outcome measure SAE are still underpowered to detect or reject a statistically significant intervention effect - but firm evidence may be obtainable by adding a new trial for both outcome measures according to the LBHIS TSA.

The LBHIS analysis on total complications shows that a clinically meaningful difference can be rejected, whereas the sensitivity APHIS analysis shows that the meta-analysis is still underpowered to detect or reject an intervention effect. With regard to all other types of complications, the meta-analyses are underpowered to detect or reject a significant intervention effect.

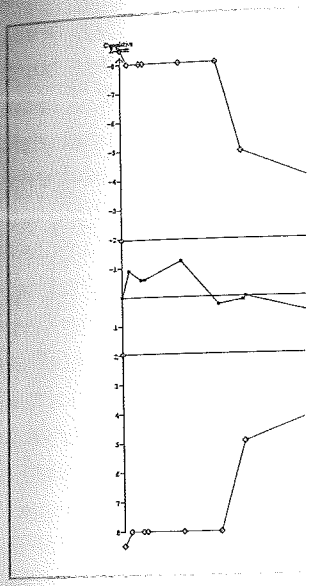

Figure 3: Trial sequential analysis o trial [31] as it provides non-dete

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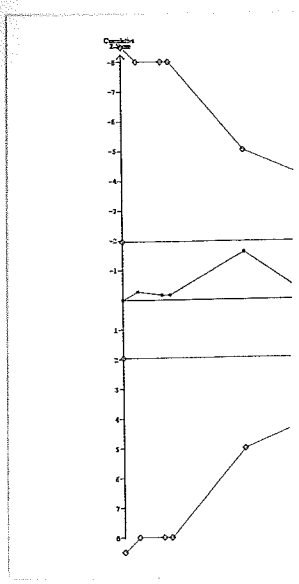

Figure 4: Trial sequential analysi in a composite outcome meas

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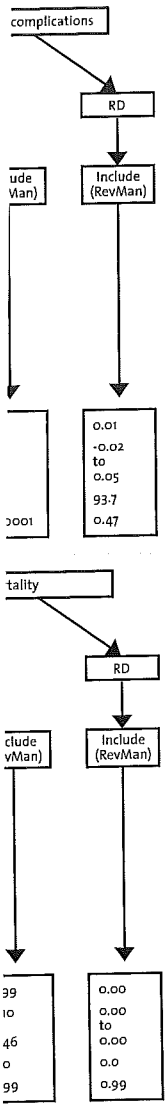

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	Number of outcomes in laparoscopic cholecystectomy (proportion)	Number of outcomes in small-incision cholecystectomy (proportion)	Total number of of outcomes (proportion)	Number of trials with data*	Number of participants	Number of zero-event trials (proportion of trials reporting data)
• Mortality	1 (0.1%)	1 (0.1%)	2 (0.1%)	7	1952	5 (71.4%)
• Intra-operative complications	153 (11.9%)	88 (6.8%)	241 (9.3%)	14	2560	10 (71.4%)
• Minor complications	98 (7.6%)	114 (8.8%)	212 (8.2%)	14	2560	3 (21.4%)
• Severe complications	48 (3.7%)	50 (3.9%)	98 (3.8%)	14	2560	4 (28.6%)
• Bile duct injuries	15 (1.2%)	22 (1.7%)	37 (1.4%)	14	2560	5 (35.7%)
• Total complications	314 (24.3%)	274 (21.2%)	588 (22.8%)	14	2560	2 (14.8%)
• Conversions to open cholecystectomy	148 (12.9%)	172 (15.1%)	320 (14.0%)	9	1952	0 (0%)

Table 1: Event proportion of binary outcome measures in a systematic review with meta-analyses of 15 trials on laparoscopic versus small-incision cholecystectomy in patients with symptomatic cholecystolithiasis.

** Eight trials did not report on mortality, one trial did not report on complications, and six trials did not report on conversions to open cholecystectomy.*

LEVEL OF CHOICE OF METHOD											
Statistical pooling method	DL RE										
Summary statistic	RR					RD	OR				
Exclude or include zero event trials	Include (CC)				Exclude (RM)	Include (RM)	Include (CC)				Exclude (RM)
Type of continuity correction	Rec		Emp		-	-	Rec		Emp		-
Value of continuity correction	1.0	0.01	1.0	0.01	-	-	1.0	0.01	1.0	0.01	-
OUTCOME MEASURES											
Mortality	1.00	0.99	0.94	0.95	0.99	0.00	1.00	0.99	0.94	0.95	1.00
Intra-operative complications #	1.71 *	1.75 *	1.74 *	1.75 *	1.74 *	0.01	2.11 *	2.25 *	2.22 *	2.26 *	2.21 *
Minor complications	0.97	1.04	0.97	1.04	0.91	-0.02	0.93	1.04	0.95	1.04	0.87
Severe complications	1.12	0.74	1.07	0.74	1.34	0.01	1.15	0.74	1.09	0.74	1.36
Bile duct injuries	0.74	0.67	0.70	0.67	0.71	0.00	0.74	0.66	0.70	0.66	0.70
Total complications	1.03	1.04	1.03	1.04	1.01	-0.01	0.98	1.00	0.98	1.00	0.96
Conversions	1.02	1.02	1.01	1.02	1.01	0.00	1.03	1.03	1.02	1.04	1.02

Table 2: Pooled effect estimates of meta-analysis of mortality, complications, and conversions using different statistical methods.

*DL RE: DerSimonian and Laird random-effects model; RR: relative risk; RD: risk difference; OR: odds ratio; CC: Continuity correction (methodology that includes zero-event trials by adding partially event fractions); RM: RevMan (Review Manager software used in Cochrane reviews that excludes zero event trials in RR and OR); Rec: reciprocal continuity correction; Emp: empirical continuity correction; *significant difference favoring small-incision cholecystectomy; #inconsistency in significance. Pooled intervention effect estimate < 1 favors laparoscopic cholecystectomy; Pooled intervention effect estimate > 1 favors small-incision cholecystectomy.*

narrow 95% confidence limits (-0.02 to 0.05) and showed no significant difference (P = 0.47). The RD analysis showed heterogeneity of 94%.

Regarding all other outcomes, all analyses concurred that no significant difference was present.

Inconsistency of confidence limits

In all outcome measures, we found variations in the width of the confidence limits. For instance, in mortality with a control event rate of 0.1%, the 95% confidence limits in RR changed from a narrow interval (0.23-3.75), using a 1.0 empirical continuity correction, to a broad interval (0.00-9.132E[17]), using a 0.001 empirical continuity correction (Figure 1b). The range of the 95% confidence limits increased to infinity with decreasing continuity corrections, in both RR and OR. In contrast, RD confidence limits were narrow (0.00-0.00).

For all other outcomes, the variations in the width of the confidence limits were less substantial.

Inconsistency of meta-analyzed intervention-effect estimates

For all outcomes, we found variations in the magnitude of the meta-analyzed intervention-effect estimates, both in RR and in OR (Table 2). For instance, a substantial variation was found in the analysis of severe complications, with RR varying from 0.74 to 1.34, corresponding to RRR varying from -26% to +34%.

When the continuity correction was varied, both the direction and the magnitude of the intervention-effect estimates in the random-effects RR and OR calculations changed with respect to minor and severe complications. For severe complications, the intervention-effect estimates shifted from favoring small-incision cholecystectomy (RR: 1.07) to favoring laparoscopic cholecystectomy (RR: 0.74) when the empirical continuity correction changed from 1.0 to 0.01.

The meta-analyzed intervention-effect estimates did not vary substantially for the other outcomes.

Sensitivity analysis

We repeated all calculations including only the low-bias risk trials without noticeable effect on our results. The inconsistency of significance in intraoperative complications persisted.

DISCUSSION

We found inconsistency in sig
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DISCUSSION

We found inconsistency in significance, confidence limits, intervention-effect estimates, and heterogeneity depending on the analysis conducted. We discovered clinically important disagreement in the interpretation of the significance in one of seven outcome measures (14%; 95% confidence limits 0.4%-57.9%). The RD analysis showed no statistically significant difference, whereas all the other analyses resulted in significantly more intraoperative complications in the laparoscopic group than in the small-incision cholecystectomy group. We observed considerable variability in the confidence limits with the size of the continuity corrections. Different meta-analytical methods resulted in varied intervention effect estimates for all examined outcomes. The differences in the confidence limits and intervention estimates may have an impact on conduct of further trials. Sample-size calculation is dependent on the control event rate and effect estimate, which are influenced by inclusion or exclusion of zero-event trials.

The RD is an analysis of real data. In RD, the weighting of the individual trial is based on the number of participants in the trial, independent of the event numbers. Consequently, trials that contribute the majority of events may be given relatively low weighting, while zero-event trials may be given relatively heavy weighting. Zero-event trials could reflect the "truth", but they could also underreport events caused by bias, random error, or short follow-up. In the RR analysis including zero-event trials, data are added artificially, which may influence reliability. In RR analyses, the weighting is related to the proportion of events by inverse variance weighting. In the relative summary statistics, trials with the majority of events are weighted more heavily than zero-event trials, which RevMan analyses exclude, or given low weighting when a continuity correction is used.

We found inconsistency in conclusions on significance in one out of seven outcomes with varying control event rates and numbers of zero-event trials. Choice of statistical analysis was made at five levels. Each choice may contribute to the varying conclusions. Consequently, the inconsistency may be due to the combination of the model, summary statistic, and continuity corrections used for zero-event data. However, the variation in distribution of events and participants might have a greater influence on conclusions depending on the method of weighting the data in the meta-analysis compared with the influence of how zero events were handled. Some outcomes without inconsistency in conclusions (e.g., mortality and bile duct injuries) showed less variation in event proportions compared with other outcomes (e.g., intraoperative and severe complications), while all outcomes included a substantial number of zero-event trials. Therefore, zero-event trials may not influence significance as much as hypothesized.

In mortality, the 95% confidence limits using a continuity correction of 0.01 (0.00-477,301) are wide, whereas those using a continuity correction of 1.0 (0.23-3.75) are unrealistically narrow considering the paucity of information. The 1.0 continuity correction adds 12 "artificial" deaths to the two deaths actually observed, risking unreliable estimates. With decreasing continuity corrections, the range of the confidence limits increased to infinity. In contrast, confidence limits in RD were suspiciously narrow (0.00-0.00). This is misleading, given that only one patient died in each intervention group. Our analyses illustrate that meta-analysis including zero-event trials on outcomes with rare events may produce highly unreliable confidence limits.

We found variation in the intervention-effect estimates, and some of it was substantial. Obviously, the event proportion in the background population and the intervention-effect estimate may greatly influence trial sample-size calculation [14,15]. The RR intervention-effect estimates with the outcome of severe complications varied from 0.74 to 1.34. Considering such an important outcome measure with an event proportion approaching 5%, an intervention effect of 26% RRR would certainly be an incentive for a new randomized trial. In contrast, a 2.0% RRR would not be. Thus, the choice of the statistical analysis influences the estimated intervention effect and hence the impetus to initiate a new trial [14,15].

A composite outcome measure of all serious events may be the most appropriate, as it includes all outcomes and yields a higher event proportion (approximately 10%). In our meta-analysis, the trial carried out by Ros et al. [22] dominates the intraoperative complications in the RR and OR meta-analyses, while in the RD model almost equal weighting is applied to all trials. A real difference in intraoperative complications across trials may be caused by heterogeneity in the populations at risk, heterogeneity in the surgeons' skills, or bias, e.g., systematic difference in registration of complications. Many of the trials did not focus on complications, which therefore may have been overlooked. Differences in the bias risk of trials might add to the differences in their reporting. Low-bias risk trials - e.g., the Ros et al. trial [22] - produce more reliable estimates. Remarkably, all the zero-event trials were high-bias risk trials [5]. Therefore, the "truth" may lie in low-bias risk trials with higher proportions of complications. The statistical heterogeneity in the RD model (94%) may therefore reflect the systematic errors related to the reporting of complications. This example illustrates the intimate linkage of statistical analysis to the clinical perspective. Thorough knowledge of the clinical setting is needed in order to draw overall statistical inference from meta-analyses.

Considering the issues arising from the zero-event data [18] and the recommendations originating from simulation studies [2,7], RevMan does not seem optimally equipped for handling zero-event trials. Moreover, RevMan is not equipped for robust assessment of

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meta-analyses including zero-event trials.

Several trials did not report certain outcomes. Such lack of reporting may represent outcome measure reporting bias, which may lead to biased overestimation of intervention effects [35]. We did not consider this bias risk.

The choice of statistical method may impact the conclusions of meta-analyses of binary data when zero-event trials are included. RevMan does not handle zero-event trials appropriately and may produce erroneous results. The choice of statistical method leads to varied estimates of confidence limits and meta-analyzed intervention-effect estimates. A priori selection of statistical methods for meta-analyses should be included in the protocol for a systematic review [16] in order to avoid wish-biased, post hoc selection of "desirable" results. Differences in estimates of intervention effects may impact the design of future trials [1,14,15]. Conducting multiple assessments of robustness may prevent spurious conclusions, reducing statistical method bias.

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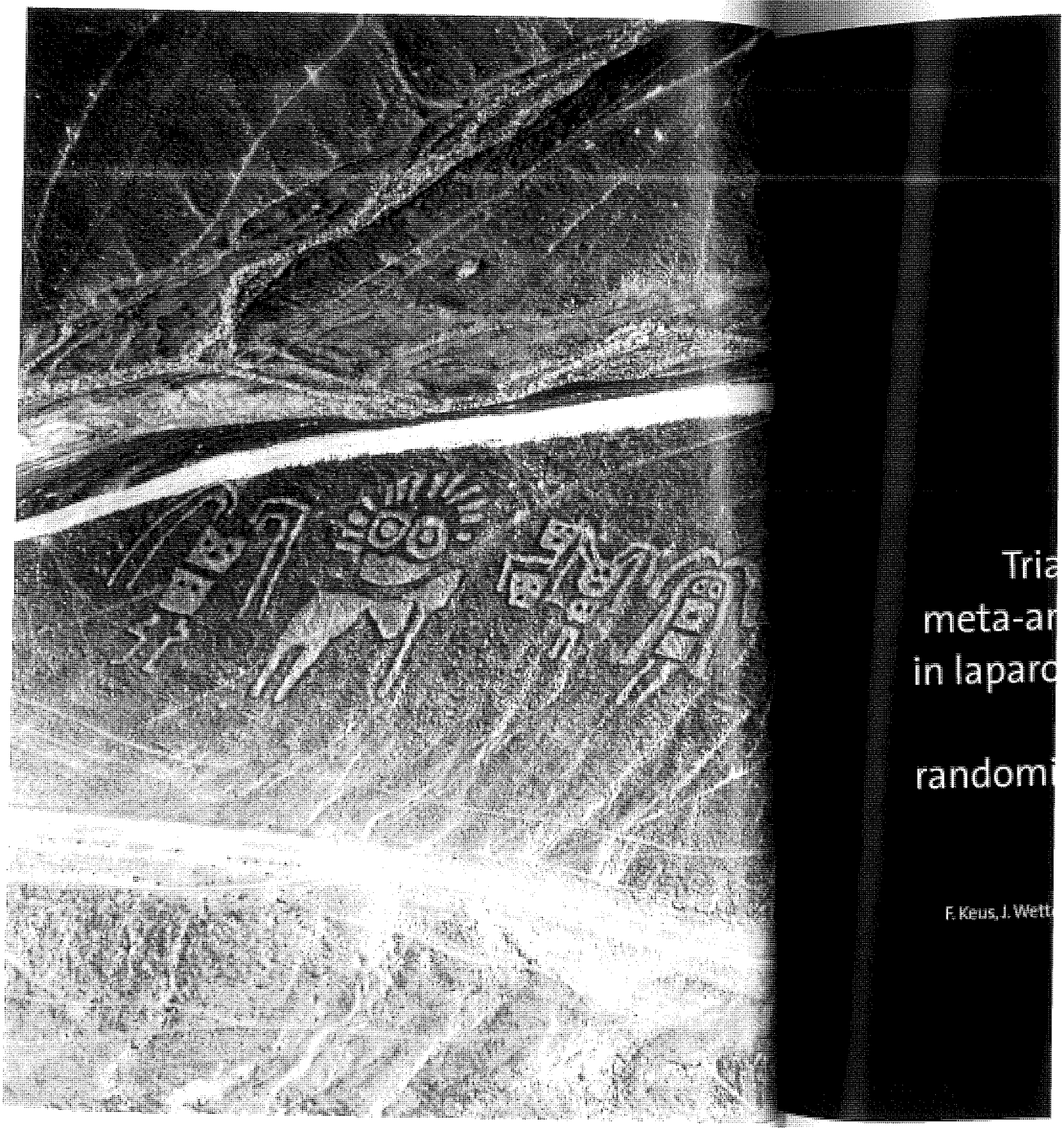
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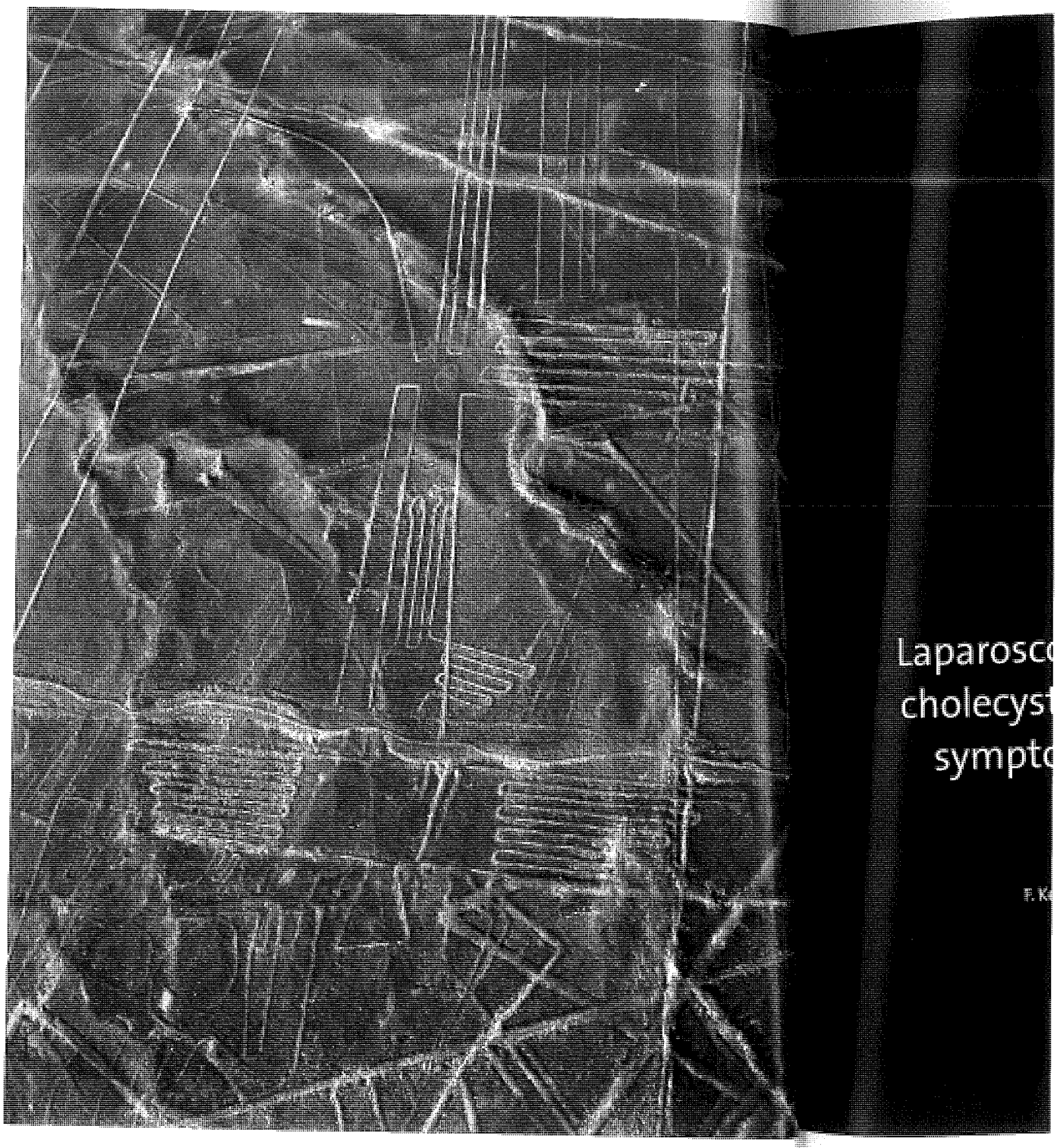
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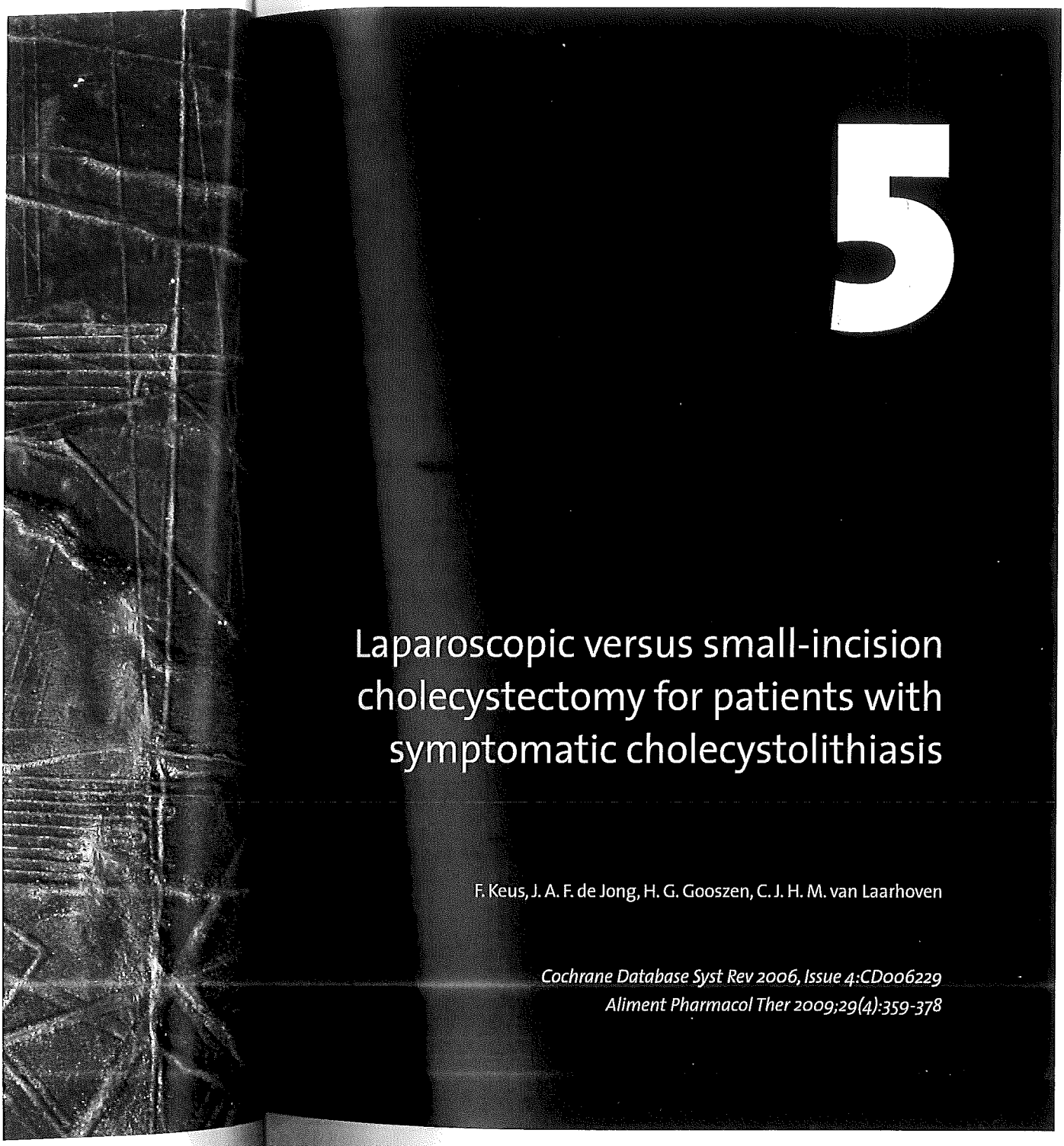

5

Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis

F. Keus, J. A. F. de Jong, H. G. Gooszen, C. J. H. M. van Laarhoven

Cochrane Database Syst Rev 2006, Issue 4:CD006229
Aliment Pharmacol Ther 2009;29(4):359-378

ABSTRACT

Background

Cholecystectomy is one of the most frequently performed operations. Open cholecystectomy has been the gold standard for over 100 years. Small-incision cholecystectomy is a less frequently used alternative. Laparoscopic cholecystectomy was introduced in the 1980s.

Objectives

To compare the beneficial and harmful effects of laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis.

Search strategy

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (6 April 2004), The Cochrane Library (Issue 1, 2004), MEDLINE (1966 to January 2004), EMBASE (1980 to January 2004), Web of Science (1988 to January 2004), and CINAHL (1982 to January 2004) for randomised trials.

Selection criteria

All published and unpublished randomised trials in patients with symptomatic cholecystolithiasis comparing any kind of laparoscopic cholecystectomy versus small-incision or other kind of minimal incision open cholecystectomy. No language limitations were applied.

Data collection and analysis

Two authors independently performed selection of trials and data extraction. The methodological quality of the generation of the allocation sequence, allocation concealment, blinding, and follow-up was evaluated to assess bias risk. Analyses were based on the intention-to-treat principle. Authors were requested additional information in case of missing data. Sensitivity and subgroup analyses were performed if appropriate.

Main results

Thirteen trials randomised 2337 patients. Methodological quality was relatively high considering the four quality criteria. Total complications of laparoscopic and small-incision cholecystectomy are high: 26.6% versus 22.9%. Total complications (risk difference, random-effects -0.01, 95% confidence interval (CI) -0.07 to 0.05), hospital stay (weighted mean difference (WMD), random-effects -0.72 days, 95% CI -1.48 to 0.04), and convalescence were not significantly different. High-quality trials show a quicker operative time for small-incision cholecystectomy (WMD, high-quality trials 'blinding', random-effects 16.4 minutes, 95% CI 8.9 to 23.8) while low-quality trials show no significant difference.

Authors' conclusions

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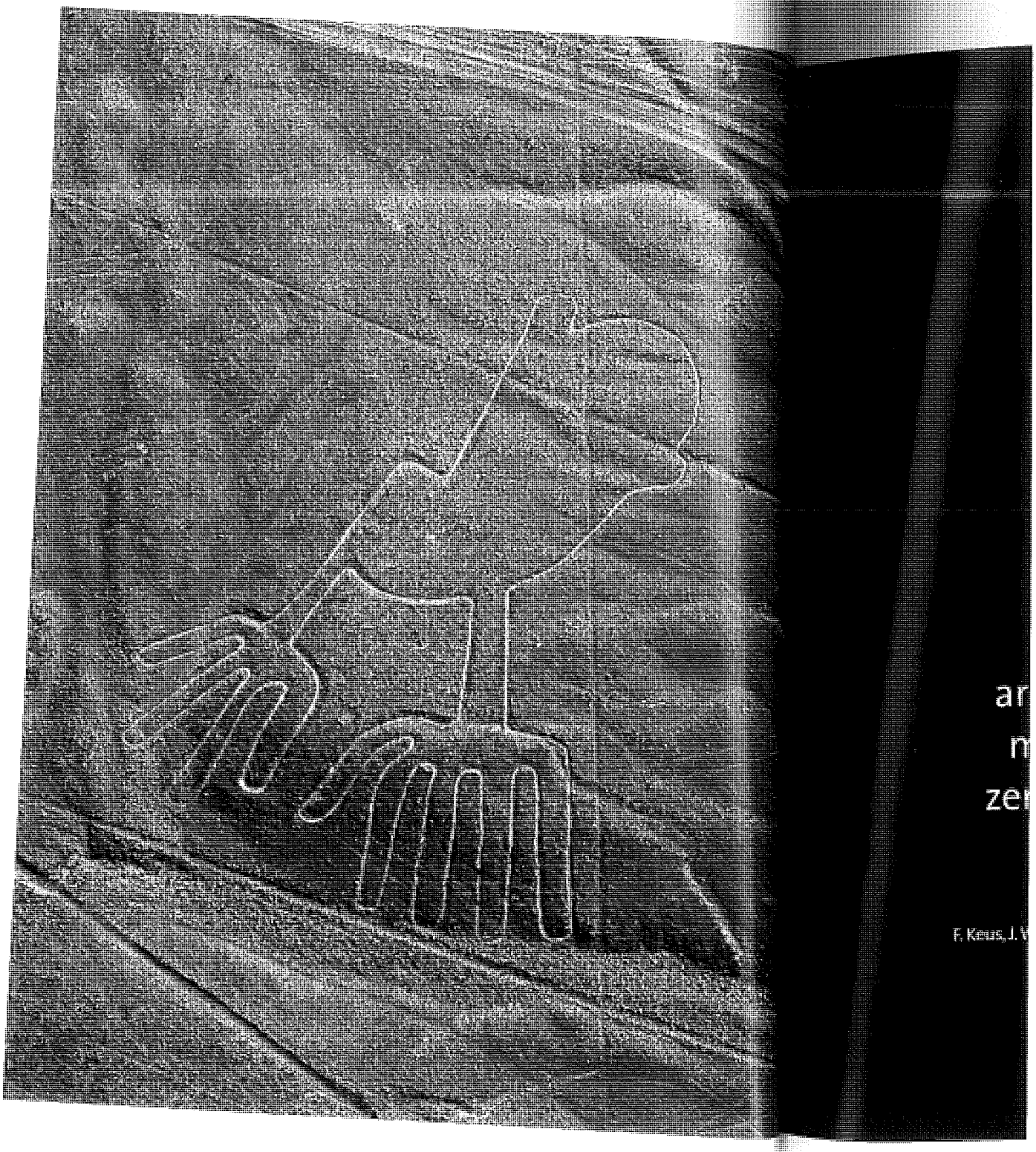
Authors' conclusions

Laparoscopic and small-incision cholecystectomy seem to be equivalent. No differences could be observed in mortality, complications, and postoperative recovery. Small-incision cholecystectomy has a significantly shorter operative time. Complications in elective cholecystectomy are prevalent.

Only the abstract rather than the full text of the Cochrane systematic review is printed here due to space limitations. The full text may be accessed at the Cochrane Library (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD006229/frame.html). Instead, the sister publication in Alimentary, Pharmacology & Therapeutics summarizing the results of chapters 3, 4, and 5 is printed on page 44.



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Robustness assessments are needed to reduce bias in meta-analyses that include zero-event randomized trials

F. Keus, J. Wetterslev, C. Gluud, H. G. Gooszen, C. J. H. M. van Laarhoven

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ABSTRACT

Objectives

Meta-analysis of randomized trials with binary data can use a variety of statistical methods. Zero-event trials may create analytic problems. We explored how different methods may impact inferences from meta-analyses containing zero-event trials.

Methods

Five levels of statistical methods are identified for meta-analysis with zero-event trials, leading to numerous data analyses. We used the binary outcomes from our Cochrane review of randomized trials of laparoscopic vs. small-incision cholecystectomy for patients with symptomatic cholecystolithiasis to illustrate the influence of statistical method on inference.

Results

In seven meta-analyses of seven outcomes from 15 trials, there were zero-event trials in 0 to 71.4% of the trials. We found inconsistency in significance in one of seven outcomes (14%; 95% confidence limit 0.4%-57.9%). There was also considerable variability in the confidence limits, the intervention-effect estimates, and heterogeneity for all outcomes.

Conclusions

The statistical method may influence the inference drawn from a meta-analysis that includes zero-event trials. Robustness assessments are needed to reduce bias in meta-analyses that include zero-event trials.

INTRODUCTION

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INTRODUCTION

Randomized trials seldom detect intervention differences when binary outcomes are rare or absent. Meta-analyses are conducted to obtain more precise estimates and to increase power to detect small, but clinically important, intervention effects. The number of systematic reviews with meta-analyses is increasing [1; www.cochrane.org]. The applied statistical methods may impact inferences. Meta-analyzing trials is problematic when no events occur in one or more trial arms [2]. Adding continuity corrections may help, but it introduces fake events and may bias inferences.

In our recently published Cochrane reviews on cholecystectomy [3-5], we included trials with rare events as well as zero events. The Cochrane Review Manager [RevMan Analyses 4.2.10; http://www.cochrane.org] ignores data from zero-event trials when calculating odds ratios and relative risks [6]. Although alternative ways of dealing with zero-event data exist, we chose risk differences as a summary statistic [2-7]. We now assess whether the inferences from one of the reviews [5] would change if other statistical methods were applied.

METHODS

The effect estimate and the confidence limits of a meta-analysis are influenced by the summary statistic [8], the statistical method of pooling data [7], the type of continuity correction [2], the value of continuity correction [2,9], and the fixed- or random-effects model [10-12] chosen. Inconsistency of results has been noted when these variables were examined individually [2,7-12]. We could not identify studies that quantified the effect of the different choices on intervention-effect estimates, confidence limits, heterogeneity (inconsistency factor, I^2) [13], statistical significance, and inference from a meta-analysis. We hypothesized that the different combinations may lead to differences in variables. Furthermore, the initiation of future trials should be based on meta-analysis of previous trials on the intervention [1,14,15]. Therefore, a precise intervention-effect estimate is important to provide valid relative risk reductions (RRRs) for use in sample-size calculation.

Choice levels

Five "choice levels" for inclusion of zero-event trials in a binary meta-analysis exist. The first is the summary statistic: relative risk (RR), odds ratio (OR), or risk difference (RD). The second refers to zero-event trials: excluded or included. The third, when included, is the type of continuity correction. The fourth is the value of continuity correction. The fifth is the method of meta-analyzing data, which must be selected from a variety of fixed-

and random-effects models [1,16,17]. The multiple options lead to hundreds of combi-nations. The type of data (e.g., small or large trials, group-size imbalance, number of events) may influence the choice. Not all combinations are suitable. The large variety of statistical choices increases the risk of a spurious but statistically significant or "desired" result. If a meta-analysis is without zero-event trials, the first- and fifth-level choices become relevant.

First level: summary statistic. The summary statistic RR, OR, or RD should be chosen. Arguments influencing the selection are consistency of effect, mathematical properties, and ease of interpretation [8]. We examined all three, as there is no absolute preference and no single statistic uniformly performs best.

Second level: exclude or include zero-event trials. Zero-event trials are frequently omitted from analyses, causing potential information loss and overestimated intervention effect [18]. Such trials may contribute significantly to the estimates of event proportions pending population risk. Omission of data may bias the results. Ethically, patients in these trials deserve inclusion.

When RR or OR is chosen, RevMan [6] automatically includes trials with zero events in one arm by adding 0.5 to each arm, but trials with zero events in both arms are omitted. Other types of software allow the inclusion of all trials, using different types and values of continuity corrections. To assess the influence of omitting zero-event trials on RR and OR, we used RevMan. To include zero-event trials, we used the Trial Sequential Analysis (TSA) program (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark) [14].

Third level: type of continuity correction. Continuity corrections are used to include zero-event trials in the calculation of RR and OR. Sweeting et al. introduced "reciprocal" and "empirical" continuity corrections as alternative methods to the addition of 0.5 and showed that the last performed worse in all situations [2]. We tested all three types.

Fourth level: size of continuity correction. Conventionally, a value of 0.5 is added to each group in a 2 x 2 table; thus, one participant is added to each intervention arm. Agresti found that smaller continuity corrections improved the estimates of the most likely ORs [9]. We tested four continuity values (1.0, 0.1, 0.01, and 0.001), half of which were added to each intervention arm. We report only the results with 1.0 and 0.01, unless otherwise stated.

Fifth level: the statistical meta-analyzing model (fixed- or random-effects model). Random-effects models may result in more cautious estimates compared with fixed-effect

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models [19], as intertrial variance is added to the sampling error of the individual trials, giving wider confidence limits. The random-effects model may be chosen when considerable heterogeneity is present, to allow for larger uncertainty. There is no strict guide as to which model to use. Because we consider the fixed-effect model a special case of the random-effects model in the absence of heterogeneity, and because the random-effects model is less susceptible to random error, we present only the results from this model, specifically the DerSimonian and Laird model [10].

Application of the statistical tests to real data

We used the data of meta-analyses on binary outcome measures from our Cochrane review on laparoscopic cholecystectomy vs. small-incision cholecystectomy for patients with symptomatic cholecystolithiasis [5]. As complications varied, we analyzed four subcategories (intraoperative, minor, severe, and bile duct injury) and total complications. Because we had the number of complications, and not the number of patients with complications, double counts were possible [5]. This may be a problem, but we estimate that less than 5% of the complications were double counts.

The effect of statistical method of analysis was evaluated by measuring the intervention-effect estimate, 95% confidence limits, heterogeneity, and statistical significance. Heterogeneity was calculated by the Cochran Q test and quantified by the I^2 [13].

Trials were defined as low-bias risk trials when at least three of the four risk domains (generation of the allocation sequence, allocation concealment, blinding, and follow-up) were adequately performed [20-22]. We repeated all calculations including only the low-bias risk trials in sensitivity analyses [20-22].

RESULTS

The meta-analyses included 15 randomized trials [20-34] with 2,582 participants: 1,291 laparoscopic cholecystectomy patients and 1,291 small-incision cholecystectomy patients [5] (Table 1). Only 46.6% to 93.3% of 15 trials reported outcomes (Table 1). Among trials reporting outcomes, 0% to 71.4% were zero-event trials.

Inconsistency of significance and heterogeneity

The meta-analysis on intraoperative complications included 10 zero-event trials, 2 trials with zero events in one intervention group, and 2 trials with events in both intervention groups (Figure 1a). We found inconsistency in significance. The RR and OR analyses showed significant effects favoring small-incision over laparoscopic cholecystectomy ($P < 0.0001$) without heterogeneity. The RD pooled intervention effect was 0.01 with

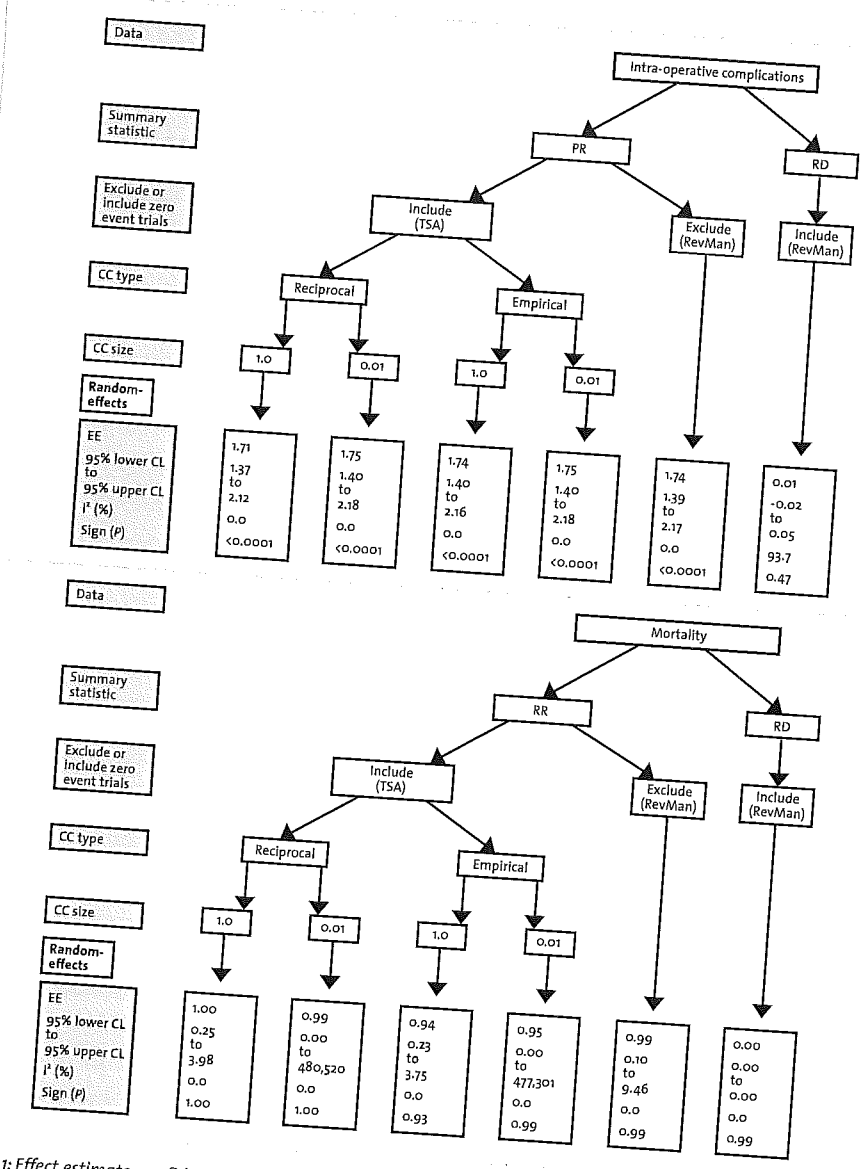

Figure 1: Effect estimate, confidence limits, heterogeneity, and significance calculated using different statistical methods including data on intra-operative complications (a) and mortality (b) of all randomised trials on laparoscopic versus small-incision cholecystectomy.

Legenda: RR: relative risk; RD: risk difference; TSA: trial sequential analysis program (including zero-event trials; developed by the Copenhagen Trial Unit, Copenhagen, Denmark); RevMan: Review Manager, software for Cochrane Reviews (excluding zero-event trials; www.cochrane.org); CC type: type of continuity correction; CC size: size of continuity correction; Random -effects: Random-effects model (DerSimonian and Laird); EE: pooled intervention effect estimate; CL: confidence limits; I^2: inconsistency factor, quantification of heterogeneity; Sign (P): significance expressed in P-value. Results of OR analyses were comparable to RR analyses and were therefore not presented. Since constant continuity corrections perform worse in all situations (2) only reciprocal and empirical continuity corrections were presented. Additionally, for reasons of simplicity 0.1 continuity corrections were not presented.

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- Severe complications 48
- Bile duct injuries 15
- Total complications 314
- Conversions to open cholecystectomy 148

Table 1: Event proportic on laparoscopic versi

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Level of choice of method
Statistical pooling method
Summary statistic
Exclude or include zero event trials
Type of continuity correction
Value of continuity correction
Outcome measures
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Intra-operative complications *
Minor complications
Severe complications
Bile duct injuries
Total complications
Conversions

Table 2: Pooled effect estimate

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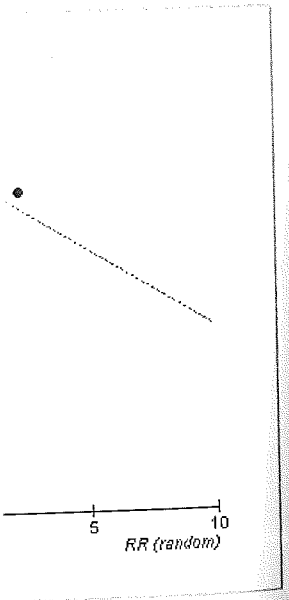

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favouring the small-incision technique.

ons were 12.9% and 15.1% in the LC and SIC group respectively. Meta-analysis of conversions including all trials shows no significant difference, while meta-analysis including low-bias risk trials shows a significant difference favouring the LC technique.

5. Operative time

Operative time was reported in 11 trials, including 2198 patients. Meta-analyses of all trials and low-bias risk trials consistently showed that SIC was significantly faster (on average 16 min) to perform than LC (Figure 7).

6. Hospital stay

Hospital stay was reported in nine trials, including 1702 patients. Meta-analysis of hospital stay including all trials shows a significant difference favouring LC (on average 0.8 day), while meta-analysis including low-bias risk trials shows no significant difference.

7. Convalescence

Limited data are available on convalescence. Three trials (all low-bias risk) including 1181 patients reported convalescence considering work leave. Meta-analysis showed no significant difference between LC and SIC considering convalescence in terms of work-leave.

Five trials including 1246 patients reported convalescence considering normal activity. Meta-analysis including all trials shows a significantly quicker convalescence considering normal activity favouring the LC technique, while low-bias risk trials do not show a significant difference.

8. Other secondary outcome measures

Insufficient data were available considering other outcomes.

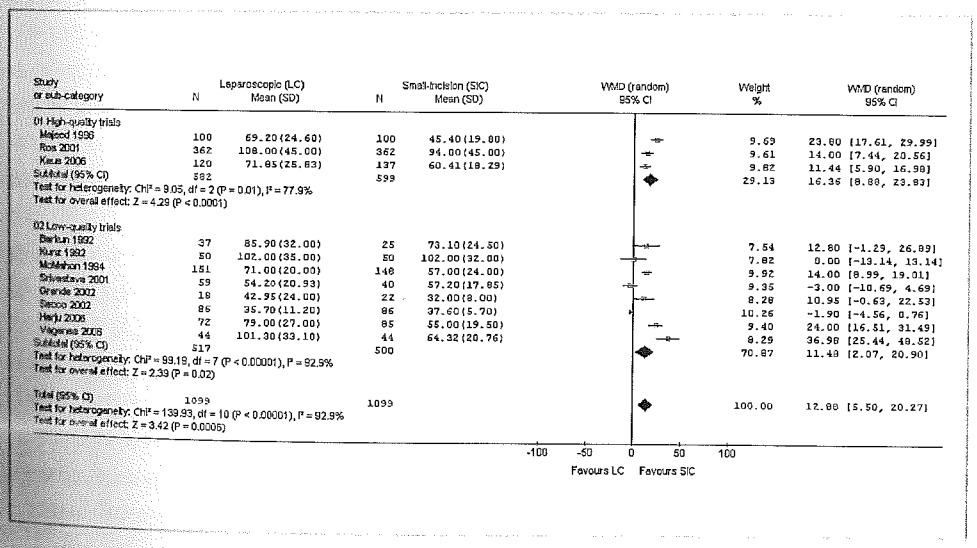

Figure 7: Forrest plot showing individual data and pooled results of operative time including all randomized trials on laparoscopic versus small-incision cholecystectomy.

DISCUSSION

A total of 59 randomized trials with varying methodological quality studied the clinical outcomes of OC, SIC, and LC. Overall, no differences were found in primary outcomes among the three techniques. Although some differences in complications were found, subgroup analyses showed no differences according to adequate methodological quality domains. Secondary outcomes show differences among the three techniques. Both minimal invasive techniques have advantages over OC in terms of convalescence. SIC and LC are comparable apart from a shorter operative time using the small-incision technique. Uncertainty remains considering conversion proportions and hospital stay.

The total numbers of patients with complications are high. Total complication proportions in the LC vs. SIC comparison are 24.3% and 21.2% respectively including intra-operative gallbladder perforations, which are generally not considered a complication. Excluding gallbladder perforations decreases total complication proportions to 15.6% and 16.4% respectively. These percentages are still higher than figures (up to 5%) known from other reviews including non-randomized series. Such studies represent lower levels of evidence [10,11,51,52]. One has to assume that especially interested and skilled surgeons conducted the trials and carried out the interventions. Everyday clinical practice and complication rates ought to be followed through clinical databases and compared with benchmark values. The situation in the real world may therefore even be worse. The complication proportions in the other two comparisons (SIC vs. OC and LC vs. OC) are substantially lower compared with the proportions in the LC vs. SIC comparison. Probably, differences in methodological quality of the trials play a role. As results from low-bias risk trials are considered more reliable [20-22], we believe that the proportions in the LC vs. SIC comparison are closer to the truth.

Three low-bias risk trials were identified in the LC vs. SIC comparison and only one in the other two comparisons. Accordingly, bias risk was relatively low in the LC vs. SIC comparison, but high in the other two comparisons. High-quality trials are more likely to estimate the 'true' effects of the interventions [20-22,53,54]. In this review, trials with unclear or inadequate methodological quality tended to show more often a positive or neutral effect of laparoscopic surgery, whereas high-quality trials were more likely to show a neutral or negative effect of laparoscopic surgery. The first example concerns operative time. In detailed subgroup analyses (according to the four methodological quality criteria), the high-quality trial subgroups showed significant differences favouring the SIC technique, while the low-quality trial subgroups do not show this difference [32]. Hospital stay is a second example. Low-quality trial subgroups as well as all trials together do show a significant difference favouring the LC technique, while high-quality trial subgroups show no significant difference between the two operations [32]. Differences in methodological quality or a loss of power may explain the differences.

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Conversion proportions including all randomized trials show no significant differences. Subgroup analysis including low-bias risk trials shows more conversions using the small-incision approach. Higher methodological quality may reflect a real difference, but it may as well represent a random effect because of a loss of power. Uncertainty remains and more randomized patients are needed to reach strong conclusions.

The question however, is whether these secondary outcomes are that important. The difference in operative time is only 16 minutes for each cholecystectomy. Regarding hospital stay, we have to remember that it is no more than a surrogate marker for convalescence and because of numerous factors influencing its length, it does not necessarily reflect objective differences between two operative procedures. Moreover, differences in hospital stay in open studies may represent bias, unless the type of surgery is blinded.

The issue in applicability is the question whether selection for randomized trials introduces bias so that participation is associated with greater risks and that outcomes are worse than expected in daily life practice. In this issue, different outcomes caused by a different (better or worse) treatment have to be distinguished from a better recording of outcomes. There is empirical evidence that participation in randomized trials does not lead to worse outcomes and that results are applicable to usual practice [55]. However, one could argue that through a more careful follow-up, outcomes are better recorded leading to more objective results.

Another issue in applicability relates to generalisability. Although several bias introducing factors can be identified, populations from the individual trials are representative of the general surgical population; trials used general and comparable inclusion criteria. Moreover, the methodological quality of the included randomized trials is relatively high making results even more reliable. We therefore believe that the results of this analysis may apply to the general surgical practice.

There are limited data on additional secondary outcomes in the included trials and several questions like pulmonary and cardiovascular consequences after surgery and more detailed questions on convalescence remain unanswered. Differences between LC and SIC in ASA III and IV patients, especially considering pulmonary and cardiovascular influences might appear substantial. Most importantly, details on costs are lacking,

which potentially may provide arguments to preferences for one of both techniques.

CONCLUSIONS

Both SIC and LC are preferred over OC based on a quicker convalescence. Both minimal invasive techniques are associated with high proportions of complications. There seems to be no significant difference in complications, although some uncertainty remains. No differences are detected in convalescence, while SIC has a shorter operative time. Uncertainty remains regarding differences in hospital stay and conversion proportions. Research should focus on costs to afford additional arguments for choosing the most valuable form of cholecystectomy.

ACKNOWLEDGEMENTS

This review represents an update of our Cochrane Reviews, which were published in The Cochrane Hepato-Biliary Group Module of The Cochrane Library in 2006 [30-32]. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms and The Cochrane Library should be consulted for the most recent version of the Review.

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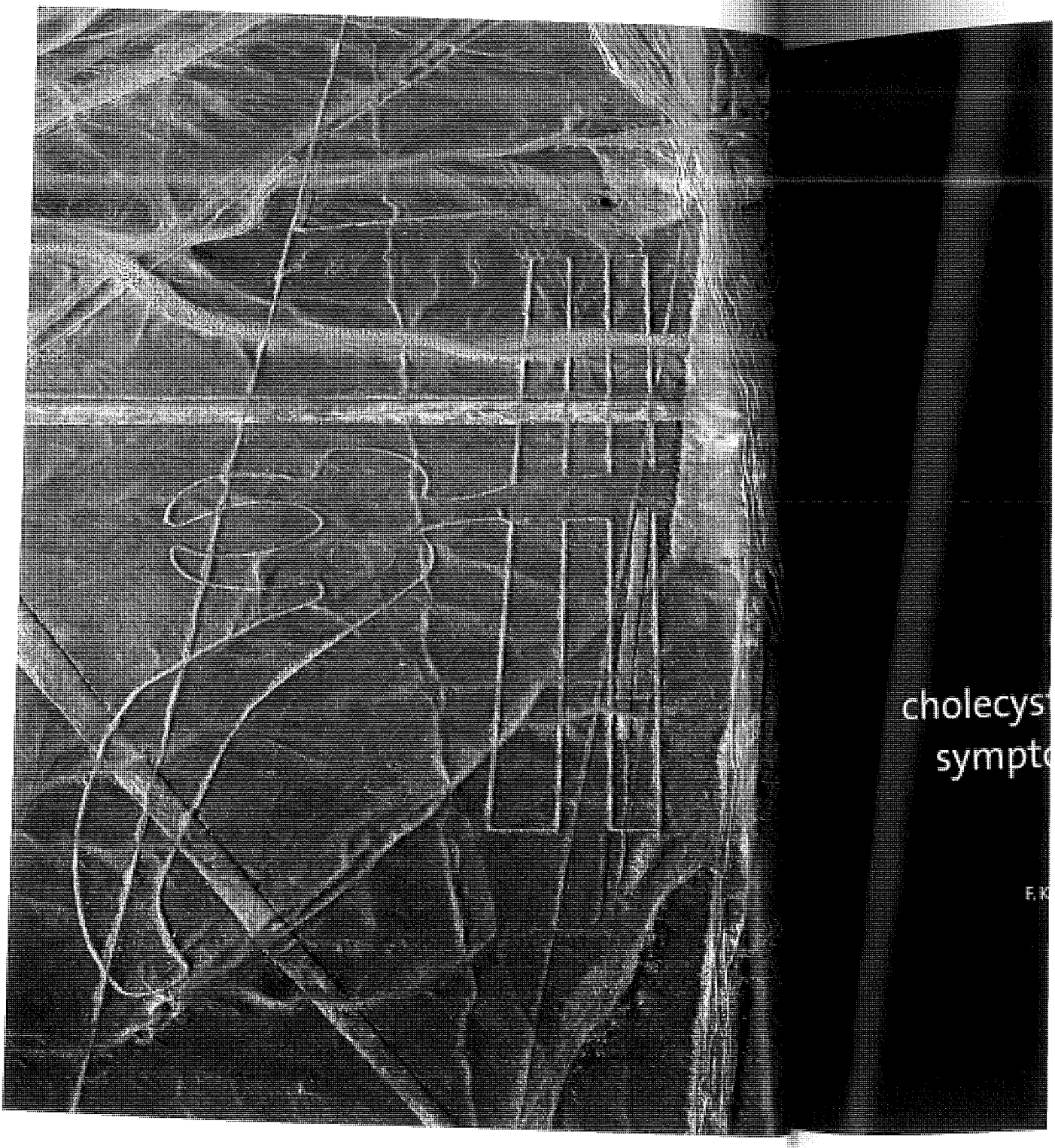

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Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis

F. Keus, J. A. F. de Jong, H. G. Gooszen, C. J. H. M. van Laarhoven

Cochrane Database Syst Rev 2006; Issue 4:CD006231
Aliment Pharmacol Ther 2009;29(4):359-378

ABSTRACT

Background

Cholecystectomy is one of the most frequently performed operations. Open cholecystectomy has been the gold standard for over 100 years. Laparoscopic cholecystectomy was introduced in the 1980s.

Objectives

To compare the beneficial and harmful effects of laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis.

Search strategy

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (April 2004), The Cochrane Library (Issue 1, 2004), MEDLINE (1966 to January 2004), EMBASE (1980 to January 2004), Web of Science (1988 to January 2004), and CINAHL (1982 to January 2004) for randomised trials.

Selection criteria

All published and unpublished randomised trials in patients with symptomatic cholecystolithiasis comparing any kind of laparoscopic cholecystectomy versus any kind of open cholecystectomy. No language limitations were applied.

Data collection and analysis

Two authors independently performed selection of trials and data extraction. The methodological quality of the generation of the allocation sequence, allocation concealment, blinding, and follow-up was evaluated to assess bias risk. Analyses were based on the intention-to-treat principle. Authors were requested additional information in case of missing data. Sensitivity and subgroup analyses were performed when appropriate.

Main results

Thirty-eight trials randomised 2338 patients. Most of the trials had high bias risk. There was no significant difference regarding mortality (risk difference 0.00, 95% confidence interval (CI) -0.01 to 0.01). Meta-analysis of all trials suggests less overall complications in the laparoscopic group, but the high-quality trials show no significant difference ('allocation concealment' high-quality trials risk difference, random-effects -0.01, 95% CI -0.05 to 0.02). Laparoscopic cholecystectomy patients have a shorter hospital stay (weighted mean difference (WMD), random-effects -3 days, 95% CI -3.9 to -2.3) and convalescence (WMD, random-effects -22.5 days, 95% CI -36.9 to -8.1) compared to open cholecystectomy.

Authors' conclusions

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Authors' conclusions

No significant differences were observed in mortality, complications, and operative time between laparoscopic and open cholecystectomy. Laparoscopic cholecystectomy is associated with a significantly shorter hospital stay and a quicker convalescence compared with the classical open cholecystectomy. These results confirm the existing preference for the laparoscopic cholecystectomy over open cholecystectomy.

Only the abstract rather than the full text of the Cochrane systematic review is printed here due to space limitations. The full text may be accessed at the Cochrane Library (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD006231/frame.html). Instead, the sister publication in Alimentary, Pharmacology & Therapeutics summarizing the results of chapters 3, 4, and 5 is printed on page 44.

Trial	Setting	Number of centres	Methodological quality: Generation of allocation sequence	Allocation concealment	Blinding	Follow-up	Randomized
Small-incision (SIC) versus open cholecystectomy (OC)							
Assalia 1993 [56]	Israel	1	U	U	N	U	50
Coelho 1992a [36]	Brasil	1	A	U	N	U	50
Coelho 1993 * [17]	Brasil	1	U	U	N	U	30*
O'Dwyer 1992a [57]	UK and Ireland	2	U	A	N	U	30
Schmitz 1997a [58]	Germany	1	U	A	N	A	130
Seenu 1994 [59]	India	1	U	U	N	U	181
Wani 2002 [60,61]	India	1	U	U	N	U	100
Total							571
Laparoscopic (LC) versus open cholecystectomy (OC)							
Agnifili 1993 [62-65]	Italy	1	U	U	N	U	50
Bellon 1998 [66,67]	Spain	1	U	U	N	U	28
Berggren 1994 [68]	Sweden	1	U	A	N	U	30
Blanc-Louvry 2000 [69]	France	1	A	U	N	U	41
Bukan 2004 [70]	Turkey	1	U	U	N	U	30
Charlo 1995 [38]	Spain	1	A	U	N	A	200
Chaudhary 1999 [71]	India	1	A	U	A	U	43
Chumillas 1998 [72]	Spain	1	U	U	N	U	40
Coelho 1993 * [17]	Brasil	1	U	U	N	U	30*
Coskun 2000 [73]	Turkey	1	U	U	N	U	70
Dauleh 1995 [74]	United Kingdom	1	U	U	N	A	78
Demirer 2000 [75]	Turkey	1	U	U	N	U	100
Dionigi 1994 [76,77]	Italy	1	U	U	N	U	57
Engin 1998 [78]	Turkey	1	U	U	N	U	32
Essen 1995 [79]	Sweden	1	U	U	N	U	12
Gal 1997 [80]	Hungary	1	U	U	N	U	42
Galizia 2001 [81]	Italy	1	U	U	N	A	33
Garcia-Caballero 1993 [45]	Spain	1	U	U	N	U	100
Hasukic 2002 [82]	Bosnia Herzegovina	1	U	A	N	U	60
Hendolin 2000 [83]	Finland	1	A	U	N	A	49
Huang 1996 [84]	Taiwan	1	U	U	N	U	29
Jan 1993 [37]	China	1	U	U	N	U	101
Ji 2005 [85]	China	1	U	U	N	U	80
Karayiannakis 1997 [86,87]	Greece	1	U	U	N	U	96
Kjaersgaard 1994 [88]	Norway	1	U	U	N	U	72
Koprulu 1996 [89]	Turkey	1	U	U	N	U	40
Lausten 1999-1 [46,47]	Egypt	1	U	U	N	U	16
Lausten 1999-2 [46,47]	Egypt	1	U	U	N	U	14
Lujan 1998 [90]	Spain	1	U	U	N	U	285
Luo 2003 [91,92]	China	1	U	U	N	U	26
Milheiro 1994 [93]	Portugal	1	U	U	N	U	40
Mimica 2000 [94]	Croatia	1	U	A	N	U	100
Ortega 1996 [95]	United States	1	A	U	A	U	20
Prisco 2000 [96]	Italy	1	U	U	N	U	25
Putensen-Himmer 1992 [97]	Austria	1	U	U	N	U	20
Rovina 1996 [98]	Greece	1	U	U	N	U	51

quality Blinding	Follow-up	Randomized	Patients excluded	Patients included Intervention	Control	Intra-operative cholangio-graphy	Antibiotic prophylaxis	Surgical expertise
				SIC	OC			
N	U	50	0	24	26	No	Y	S
N	U	50	0	25	25	Y	U	U
N	U	30*	0	15	15	U	U	U
N	U	30	0	16	14	Y	U	R
N	A	130	0	65	65	U	U	U
N	U	181	0	97	84	U	U	R
N	U	100	0	50	50	U	U	U
		571	**0**	**292**	**279**			
				LC	OC			
N	U	50	0	29	21	Y	U	U
N	U	28	0	14	14	No	U	U
N	U	30	3	15	12	No	No	SS
N	U	41	0	25	16	Y	U	S
N	U	30	0	15	15	U	U	U
N	U	200	0	100	100	U	U	U
A	A	43	0	21	22	U	Y	U
N	U	40	0	20	20	No	Uo	U
N	U	30*	0	15	15	U	U	U
N	U	70	0	35	35	U	U	U
N	U	78	0	40	38	U	No	S
N	A	100	0	50	50	No	No	SS
N	U	57	0	30	27	No	U	SS
N	U	32	0	16	16	U	U	SS
N	U	12	0	6	6	Y	U	U
N	U	42	0	21	21	U	Y	U
N	U	33	18	10	5	U	U	U
A	A	100	4	20	76	U	U	S
N	U	60	2	30	28	U	U	SS
N	U	49	2	25	22	No	U	S
N	U	29	2	15	12	U	U	U
N	A	101	0	50	51	U	U	U
N	U	80	0	38	42	U	U	U
N	A	96	9	45	42	U	U	SS
N	A	72	2	35	35	U	U	U
N	U	40	0	20	20	U	U	U
N	U	16	2	7	7	No	U	SS
N	U	14	0	7	7	No	U	SS
N	U	285	21	133	131	Y	Y	U
N	U	26	0	14	12	U	U	U
N	U	40	0	20	20	No	U	U
N	U	100	0	50	50	U	U	U
A	U	20	0	10	10	No	U	U
N	U	25	5	10	10	Y	U	U
N	U	20	0	10	10	U	U	U
N	U	51	0	26	25	U	U	SS

Trial	Setting	Number of centres	Methodological quality: Generation of allocation sequence	Allocation concealment	Blinding	Follow-up	Randomized	Patients excluded
Trondsen 1993 [99]	Norway	1	U	U	N	U	72	2
Volpino 1998 [100]	Italy	1	U	U	N	U	120	2
Zajac 1998 [101]	Poland	1	U	U	N	U	110	0
Zulfikaroglu 2002 [34]	Turkey	1	U	U	N	U	50	0
Total							2492	74
Laparoscopic (LC) versus small-incision cholecystectomy (SIC)								
Barkun 1992 [102]	Canada	5	A	U	N	A	70	8
Bruce 1999 [103]	United Kingdom	1	A	A	N	U	22	0
Coelho 1993 [17]	Brasil	1	U	U	N	U	30*	0
Grande 2002 [104]	Italy	1	U	A	N	U	40	0
Harju 2006 [105]	Finland	1	U	A	A	A	157	0
Keus 2007 [49]	Netherlands	1	A	U	N	U	264	7
Kunz 1992 [106]	Germany	1	U	A	A	A	100	0
Majeed 1996 [16]	United Kingdom	1	U	A	N	A	203	3
McGinn 1995 [18]	United Kingdom	1	U	A	N	A	310	0
McMahon 1994 [41]	United Kingdom	5	U	A	N	A	302	3
Ros 2001 [19]	Sweden	5	U	A	N	A	726	2
Secco 2002 [35]	Italy	1	U	A	N	A	181	9
Srivastava 2001 [50]	India	1	U	A	N	A	100	1
Tate 1993 [33]	Hong Kong	1	U	A	N	A	22	0
Vagenas 2006 [107]	Greece	1	A	U	N	U	88	0
Total							2615	33

Table 2: Details on setting, methodological quality, numbers of included patients, and interventions in the included randomized trials in the three comparisons evaluating techniques of cholecystectomy for symptomatic cholecystolithiasis.

Surgical interventions

An incision length of 8 centimetres was taken as cut-off between SIC and OC [16-19]. Some trials using the SIC technique did not mention the size of the incision. We classified these trials based on how the author labelled the operation. Two trials performed SIC by a 5-cm vertical (midline) incision [35,48], the others by a transverse incision in the right hypochondrium, some with muscle splitting [49], others by transsection of the rectus or oblique muscles [16,50]. OC included all procedures with an incision length exceeding 8 cm, either by vertical or transverse incision.

Usually, LC was not further specified. Some trials stated that a four trocar technique was used, creating a pneumoperitoneum by using carbon dioxide insufflations with a maximum intraperitoneal pressure of 12-15 mL mercury.

Data on the use c
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cholangiography (

Small-incision vs.
We included eig
between SIC (29

We assessed ad
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(0%), and follow
scored adequate

logical quality on ment	Blinding	Follow-up	Randomized	Patients excluded	Patients included Intervention	Control	Intra-operative cholangio-graphy	Antibiotic prophylaxis	Surgical expertise
	N	U	72	2	35	35	U	U	U
	N	U	120	2	58	60	U	U	U
	N	U	110	0	58	52	U	U	U
	N	U	50	0	25	25	U	U	U
			2492	**74**	**1203**	**1215**			
					LC	SIC			
	N	A	70	8	37	25	No	Y	SS
	N	U	22	0	11	11	U	Y	SS
	N	U	30*	0	15	15	U	U	U
	N	U	40	0	18	22	No	Y	U
	N	U	157	0	72	85	No	U	R
	A	A	264	**7**	120	137	No	Y	R
	N	U	100	0	50	50	U	U	U
	A	A	203	3	100	100	Y	U	SS
	N	A	310	0	155	155	No	U	R
	N	A	302	3	151	148	No	Y	R
	A	A	726	2	362	362	Y	U	R
	N	A	181	9	86	86	No	Y	S
	N	A	100	1	59	40	No	U	SS
	A	U	22	0	11	11	U	U	SS
	N	U	88	0	44	44	U	U	SS
			2615	**33**	**1291**	**1291**			

ions in the included randomized
natic cholecystolithiasis.

** Three-armed trial. A = adequate; U = unknown; N = not performed; Y = yes; S = one surgeon; SS = several surgeons; R = also registrars.*

en SIC and OC [16-19].
the incision. We classi-
1. Two trials performed
transverse incision in
ers by transsection of
with an incision length

four trocar technique
de insufflations with a

Data on the use of antibiotic prophylaxis, surgical experience (one or a few highly experienced surgeons performing all operations or also involving registrars), and intra-operative cholangiography (attempted in all or only in selected patients) were recorded as well (Table 2).

Small-incision vs. open cholecystectomy

We included eight publications describing seven trials randomizing 571 patients between SIC (292) and OC (279) [30].

We assessed adequate methodological quality as follows: generation of allocation sequence one trial (14.3%), allocation concealment two trials (28.6%), blinding no trials (0%), and follow-up one trial (14.3%). All trials were high-bias risk trials, as no trial scored adequate in three or more methodology criteria.

	Small-incision (SIC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus small-incision cholecystectomy (SIC)	
	SIC (n=292)	OC (n=279)	LC (n=1203)	OC (n=1215)	LC (n=1291)	SIC (n=1291)
INTRA-OPERATIVE	(0)	(0)	(10 / 0.8%)	(1 / 0.1)	(153 / 11.9%)	(88 / 6.8%)
• gallbladder perforation			7	1	112	62
• bleeding			2		23	19
• stone in common bile duct						1
• stone left in abdomen					10	
• vascular injury (hepatic artery)						1
• bowel injury					5	3
• hepatic injury					1	1
• cardiac					1	1
• cerebrovascular					1	
• other (not specified)			1			
POSTOPERATIVE-MINOR	(25 / 8.6%)	(19 / 6.8%)	(27 / 2.2%)	(40 / 3.3%)	(98 / 7.6%)	(114 / 8.8%)
• retained bile duct stone (ERCP)			1	2	4	1
• subcutaneous emphysema					1	
• wound infection	12	15	4	19	36	55
• wound haematoma	12	4	3		6	
• urinary retention	1				8	18
• urinary tract infection			8	9	5	14
• phlebitis			3	4	3	
• dyspeptic syndrome					11	12
• readmission (abdominal pain)			2			
• other (not specified)			6	6	24	14
POSTOPERATIVE-SEVERE	(4 / 1.4%)	(7 / 2.5%)	(31 / 2.6%)	(91 / 7.5%)	(48 / 3.7%)	(50 / 3.9%)
• bleeding: drainage / blood transfusion			4	1	11	4
• bleeding: re-operation			2		6	3
• stone left in cystic duct (re-operation)	1					
• biliary fistula (unspecified / conservative)			1	1		
• ileus (re-operation)					1	2
• ileus (conservative)			4	9	1	
• platzbauch				3		
• pancreatitis					3	6
• abscess (drainage / unspecified)			1	2	2	5
• abscess (re-operation)					1	1
• pneumonia	1	5	7	22	14	20
• atelectasis	1		6	35		
• septic shock				1	2	
• septic shock (re-operation)						1
• cardiovascular	1			5	2	6
• cerebrovascular accident				1	1	1
• encephalopathy			1	2		
• upper GI bleeding (endoscopy / conservative)		2	1	3		
• hernia cicatricalis						
• epididymitis (re-operation)						
• other (not specified)						
BILE DUCT INJURY						
• cystic duct leakage: drainage / ERCP						
• cystic duct leakage: re-operation						
• accessory duct leakage (re-operation)						
• minor common bile duct injury (intra-operative)						
• major common bile duct injury: re-operation						
• hepatic duct injury (intra-operative)						
• bile leakage (origin unknown): conservative						
• bile leakage (origin unknown): re-operation						
TOTAL COMPLICATIONS						
• Re-operations (all complications)						

Table 3: Detailed overview of the type of complications including all randomized trials in the three comparisons evaluating techniques of cholecystectomy for symptomatic cholecystolithiasis.

Primary outcome me

1. Mortality

None of the trials re

2. Complications

In all seven trials, inc

We found no signifi

2a. Intra-operative c

Zero intra-operative

2b. Minor complicati

The minor complica

the open group.

2c. Severe complicat

The severe complica

open group.

	Laparoscopic (LC) versus small-incision cholecystectomy (SIC)	
	LC (n=1291)	SIC (n=1291)
	(153 / 11.9%)	(88 / 6.8%)
	112	62
	23	19
		1
	10	
		1
	5	3
	1	1
	1	1
	1	
	(98 / 7.6%)	(114 / 8.8%)
	4	1
	1	
	36	55
	6	
	8	18
	5	14
	3	
	11	12
	24	14
	(48 / 3.7%)	(50 / 3.9%)
	11	4
	6	3
	1	2
	1	
	3	6
	2	5
	1	1
	14	20
	2	
		1
	2	6
	1	1

in the three comparisons
olithiasis.

	Small-incision (SIC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus small-incision cholecystectomy (SIC)	
	SIC (n=292)	OC (n=279)	LC (n=1203)	OC (n=1215)	LC (n=1291)	SIC (n=1291)
• hernia cicatricalis					3	1
• epididymitis (re-operation)					1	
• other (not specified)			4	6		
BILE DUCT INJURY	(0)	(0)	(2 / 0.2%)	(2 / 0.2%)	(15 / 1.2%)	(22 / 1.7%)
• cystic duct leakage: drainage / ERCP				1	3	1
• cystic duct leakage: re-operation						3
• accessory duct leakage (re-operation)						1
• minor common bile duct injury (intra-operative)					5	3
• major common bile duct injury: re-operation					3	2
• hepatic duct injury (intra-operative)						1
• bile leakage (origin unknown): conservative			2	1	2	8
• bile leakage (origin unknown): re-operation					2	3
TOTAL COMPLICATIONS	29 (9.9%)	26 (9.3%)	70 (5.8%)	134 (11.0%)	314 (24.3%)	274 (21.2%)
• Re-operations (all complications)	2 (0.7%)	0	3 (0.2%)	3 (0.2%)	20 (1.5%)	18 (1.4%)

Primary outcome measures

1. Mortality

None of the trials reported clearly on mortality.

2. Complications

In all seven trials, including 571 patients, complications were explicitly reported (Table 3). We found no significant differences in all complication categories (Table 4).

2a. Intra-operative complications

Zero intra-operative complications were reported.

2b. Minor complications

The minor complication proportions were 8.6% in the small-incision group vs. 6.8% in the open group.

2c. Severe complications

The severe complication proportions were 1.4% in the small-incision group vs. 2.5% in the open group.

	Small-incision (SIC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus open cholecystectomy (OC)		Laparoscopic (LC) versus small-incision cholecystectomy (SIC)			
					All randomized trials		Low-bias risk trials	
Primary outcomes								
• Mortality	n.a.		FE	0.84 (0.34 to 2.08)	FE	0.94 (0.26 to 3.40)	FE	1.04 (0.11 to 10.30)
• Intra-operative complications								
• Minor complications	FE	0.97 (0.22 to 4.24)	FE	1.40 (0.71 to 2.78)	FE	1.73 (1.30 to 2.31) *	FE	1.76 (1.31 to 2.37) *
• Severe complications	FE	1.23 (0.67 to 2.26)	FE	0.71 (0.49 to 1.04)	FE	0.86 (0.66 to 1.10)	FE	1.01 (0.70 to 1.45)
• Bile duct injuries	FE	0.67 (0.27 to 1.63)	FE	0.43 (0.33 to 0.57) *	FE	0.95 (0.65 to 1.38)	RE	1.37 (0.34 to 5.51)
• Total complications	FE	0.97 (0.22 to 4.24)	FE	0.95 (0.49 to 1.84)	FE	0.65 (0.39 to 1.10)	FE	0.82 (0.35 to 1.93)
	RE	0.98 (0.45 to 2.16)	FE	0.55 (0.43 to 0.70) *	RE	1.03 (0.73 to 1.46)	FE	1.31 (1.07 to 1.60) *
Secondary outcomes								
• Conversions					RE	1.01 (0.70 to 1.46)	RE	0.72 (0.58 to 0.91) *
• Operative time (minutes)	FE	1.94 (-1.37 to 5.25)	RE	3.79 (-4.88 to 12.46)	RE	12.88 (5.50 to 20.27) *	RE	16.36 (8.88 to 23.83) *
• Hospital stay (days)	RE	-2.78 (-4.94 to -0.62) *	RE	-3.07 (-3.89 to -2.26) *	RE	-0.81 (-1.17 to -0.45) *	FE	-0.26 (-0.69 to 0.17)
• Convalescence: work leave (days)	n.a.		RE	-22.51 (-36.89 to -8.13) *	RE	-0.43 (-4.37 to 3.51)	RE	-0.43 (-4.37 to 3.51)
• Convalescence: normal activity (at home) (days)	n.a.		n.a.		RE	-2.92 (-5.61 to -0.24) *	RE	0.79 (-5.96 to 7.55)

Table 4: Pooled effect estimates (with 95% confidence intervals) of primary and secondary outcomes including all randomized trials in the three comparisons evaluating techniques of cholecystectomy for symptomatic cholecystolithiasis.

*n.a. = no data available. FE: Fixed-effect; RE: Random-effects; * Significant differences; 95% Confidence limits in brackets. All complications are expressed in relative risks. Operative time, hospital stay, and convalescence are expressed in weighted mean differences. All relative risks were calculated using continuity corrections of 0.1 and 0.01 did not change the results in any way. In the three comparisons, pooled intervention effect estimates > 1 favour the open, open, and small-incision technique, in the three comparisons, respectively.*

2d. Bile duct injuries
Zero bile duct injurie
2e. Total complicatio
The total complicati
the open group.
3. Symptom relief
No trial reported reli

Secondary outcome
4. Operative time
Three trials includin
was found between
imputing missing da
5. Hospital stay
Two trials including
hospital stay favouri
only two trials. A se
of a significant shor
6. Other secondary o
Insufficient data we

Laparoscopic vs. ope
We included 47 pub
LC (1203) and OC (12

We assessed adequ
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(7.7%), and follow-up
performed as only c

Primary outcome m
1. Mortality
Mortality was expli
death in the OC gro
in the laparoscopic
2. Complications
Complications were
2a. Intra-operative c
Intra-operative com
respectively, withou

2d. Bile duct injuries

Zero bile duct injuries were reported.

2e. Total complications

The total complication proportions were 9.9% in the small-incision group vs. 9.3% in the open group.

3. Symptom relief

No trial reported relief of symptoms.

Secondary outcome measures

4. Operative time

Three trials including 210 patients reported operative time. No significant difference was found between the small-incision and open techniques. In a sensitivity analysis imputing missing data, there was no significant difference either (data not shown).

5. Hospital stay

Two trials including 180 patients reported hospital stay. There was a significantly shorter hospital stay favouring the small-incision technique. However, this concerns the data of only two trials. A sensitivity analysis with imputing missing data supports the finding of a significant shorter hospital stay in the small-incision group (data not shown).

6. Other secondary outcome measures

Insufficient data were available considering other outcomes.

Laparoscopic vs. open cholecystectomy

We included 47 publications describing 39 trials randomizing 2418 patients between LC (1203) and OC (1215) [31].

We assessed adequate methodological quality as follows: generation of allocation sequence five trials (12.8%), allocation concealment 10 trials (25.6%), blinding three trials (7.7%), and follow-up six trials (15.4%). No comparison of high vs. low-bias risk trials was performed as only one trial scored adequate in three or more methodology criteria.

Primary outcome meaures

1. Mortality

Mortality was explicitly mentioned in 13 trials including 987 patients. There was one death in the OC group out of 485 patients compared with 0 deaths out of 502 patients in the laparoscopic group.

2. Complications

Complications were explicitly reported in 30 trials, including 1965 patients.

2a. Intra-operative complications

Intra-operative complications were 0.8% and 0.1% in the laparoscopic and open group, respectively, without significant difference.

Primary outcomes
• Mortality

Small-incision (SIC) versus open cholecystectomy (OC)

n.a.

Laparoscopic (LC) versus open cholecystectomy (OC)

FE 0.84 (0.34 to 2.08)

Laparoscopic (LC) versus small-incision cholecystectomy (SIC)

All randomized trials

FE 0.94 (0.26 to 3.40)

Low-bias risk trials

FE 1.04 (0.11 to 10.30)

FE 1.76 (1.31 to 2.37) *

2b. Minor complications

The minor complication proportions in the laparoscopic and open groups (2.2% and 3.3% respectively) were not significantly different.

2c. Severe complications

The severe complication proportions were 2.6% and 7.5% in the laparoscopic and open group respectively. Meta-analysis of all trials showed a significant difference favouring the laparoscopic technique, while meta-analysis in subgroups according to adequate methodological quality showed no significant difference.

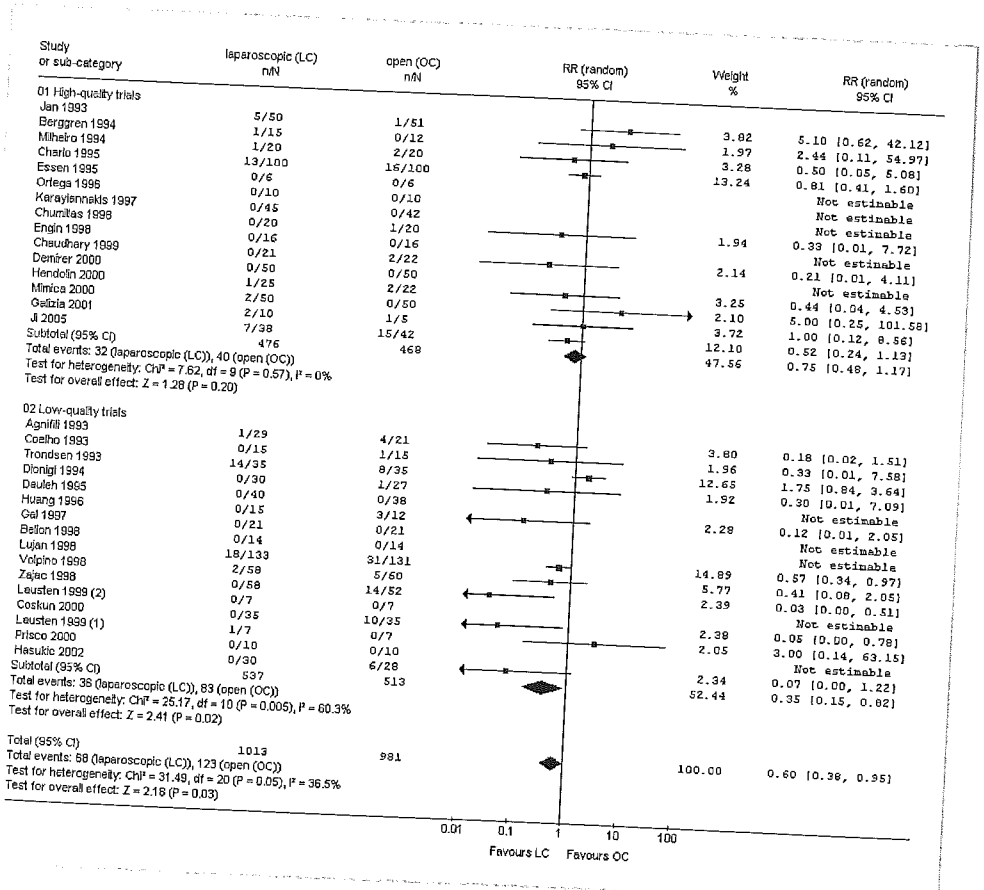

Figure 2: Forrest plot showing individual data and pooled results of total complications including all trials on laparoscopic versus open cholecystectomy.

Forrest plot was constructed using RevMan (www.cochrane.org), while calculations were performed using Trial Sequential Analysis software as RevMan does not allow using continuity corrections. Therefore, pooled estimates and confidence intervals differ slightly from results in Table 4, while the overall significant and non-significant findings concur. The squares indicate individual trial results in the form of estimated relative risks; the horizontal lines through them represent 95% confidence intervals for each trial. The sizes of the squares indicate the weight that each study contributes to the pooled estimate of the meta-analysis. The diamond at the bottom of the plot represents the pooled relative risk and the 95% confidence interval.

2d. Bile duct injuries

Bile duct injuries were

2e. Total complications

The total complicatior the open group. Meta the laparoscopic techr methodological qualit In a funnel plot using considering the absen

3. Symptom relief

Insufficient data on re

Secondary outcome m

4. Operative time

Operative time was re cant differences betw there was no significa

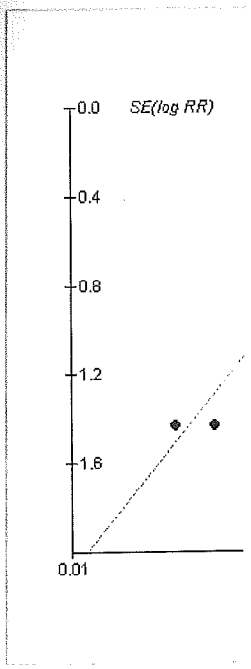

Figure 3: Funn

There is some suspicion of bic

en groups (2.2% and

ıparoscopic and open
: difference favouring
:cording to adequate

ght	RR (random) 95% CI
.82	5.10 [0.62, 42.12]
.97	2.44 [0.11, 54.97]
.28	0.50 [0.05, 5.08]
.24	0.81 [0.41, 1.60]
	Not estimable
	Not estimable
	Not estimable
..94	0.33 [0.01, 7.72]
	Not estimable
:.14	0.21 [0.01, 4.11]
	Not estimable
3.25	0.44 [0.04, 4.53]
2.10	5.00 [0.25, 101.58]
3.72	1.00 [0.12, 8.56]
2.10	0.52 [0.24, 1.13]
7.56	0.75 [0.48, 1.17]
3.80	0.18 [0.02, 1.51]
1.96	0.33 [0.01, 7.58]
2.65	1.75 [0.84, 3.64]
1.92	0.30 [0.01, 7.09]
	Not estimable
2.28	0.12 [0.01, 2.05]
	Not estimable
	Not estimable
14.89	0.57 [0.34, 0.97]
5.77	0.41 [0.08, 2.05]
2.39	0.03 [0.00, 0.51]
	Not estimable
2.38	0.05 [0.00, 0.78]
2.05	3.00 [0.14, 63.15]
	Not estimable
2.34	0.07 [0.00, 1.22]
52.44	0.35 [0.15, 0.82]
.00.00	0.60 [0.38, 0.95]

itions including all trials

performed using Trial Sequential
ıoled estimates and confidence
-significant findings concur.
al lines through them represent 95%
ı contributes to the pooled estimate
sk and the 95% confidence interval.

Chapter 3, 4, 5

2d. Bile duct injuries

Bile duct injuries were 0.2% in each group without significant difference.

2e. Total complications

The total complication proportions were 5.8% in the laparoscopic group and 11.0% in the open group. Meta-analysis of all trials showed a significant difference favouring the laparoscopic technique, while meta-analysis in subgroups according to adequate methodological quality domains showed no significant difference (Figure 2).

In a funnel plot using data on total complications, there was some suspicion of bias considering the absence of small trials favouring the open technique (Figure 3).

3. Symptom relief

Insufficient data on relief of symptoms were available.

Secondary outcome measures

4. Operative time

Operative time was reported in 23 trials, including 1134 patients. There were no significant differences between LC and OC. In a sensitivity analysis imputing missing data, there was no significant difference either (data not shown).

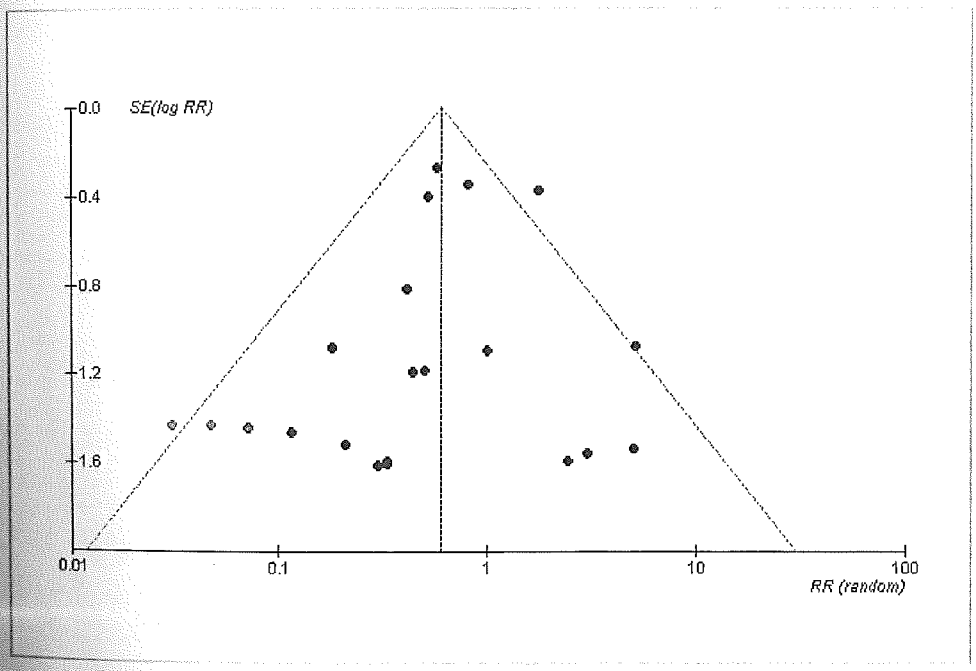

Figure 3: Funnel plots using data of total complications including 95% confidence interval lines. Laparoscopic versus open cholecystectomy.

There is some suspicion of bias considering the absence (in the lower right part) of small trials favoring the open technique.

5. Hospital stay

Hospital stay was reported in 20 trials including 1111 patients. There was a significantly shorter hospital stay favouring the laparoscopic technique (Figure 4).

6. Convalescence

Three trials including 328 patients reported convalescence considering work leave. The laparoscopic technique showed a significantly quicker convalescence.

7. Other secondary outcome measures

Insufficient data were available considering other outcomes.

Laparoscopic vs. small-incision cholecystectomy

We included 37 publications describing 15 trials randomizing 2582 patients with 1291 patients in each group [32].

We assessed adequate methodological quality as follows: generation of allocation sequence four trials (26.7%), allocation concealment nine trials (60.0%), blinding four trials (26.7%), and follow-up eight trials (53.3%). There were three low-bias risk trials. Pooled results including all trials were compared to pooled results including low-bias risk trials.

Primary outcome measures

1. Mortality

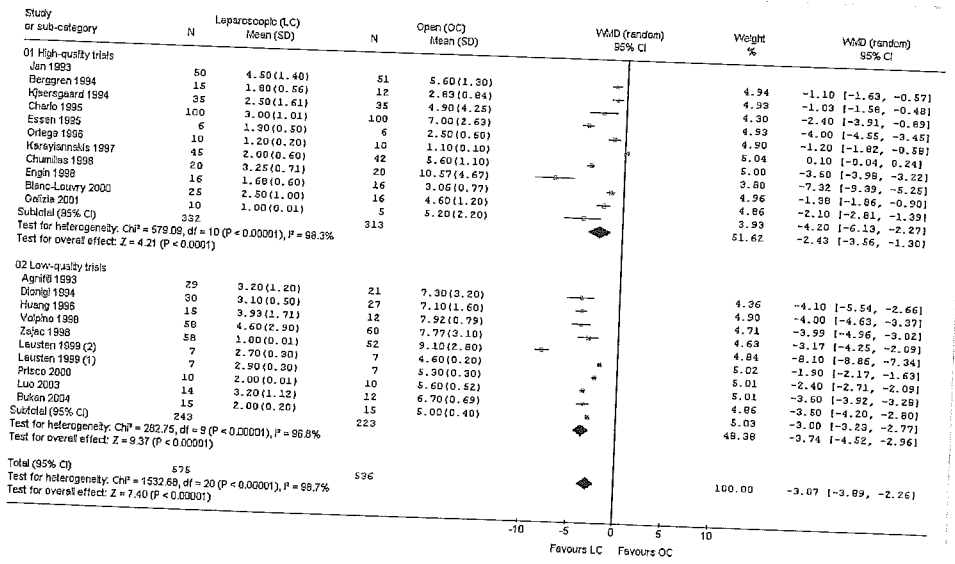

Figure 4: Forrest plot showing individual data and pooled results of hospital stay including all trials on laparoscopic versus open cholecystectomy.

Mortality was explicitl
one death in each inte
2. Complications
Complications were ex
2a. Intra-operative com
Intra-operative compli
and 6.8% respectively.
consisted of gallbladde
significantly lower in t
2b. Minor complicatio
The minor complicatic
group without signific
2c. Severe complicatio
Severe complications
significant difference.
2d. Bile duct injuries
Bile duct injuries were
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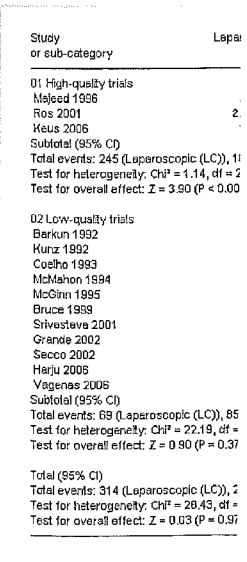

Figure 5: Forrest plot

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re 4).

dering work leave. The
ence.

582 patients with 1291

neration of allocation
(60.0%), blinding four
w-bias risk trials. Pooled
ding low-bias risk trials.

Mortality was explicitly mentioned in seven trials including 1952 patients. There was one death in each intervention group.

2. Complications

Complications were explicitly reported in 14 trials including 2560 patients.

2a. Intra-operative complications

Intra-operative complications in the laparoscopic and small-incision groups were 11.9% and 6.8% respectively. A majority of the events were accounted for by the trial of Ros and consisted of gallbladder perforations [19]. Intra-operative complication proportions were significantly lower in the SIC group.

2b. Minor complications

The minor complication proportions were 7.6% and 8.8% respectively in the LC and SIC group without significant difference.

2c. Severe complications

Severe complications were 3.7% and 3.9% in the LC and SIC group respectively, without significant difference.

2d. Bile duct injuries

Bile duct injuries were 1.2% and 1.7% in the LC and SIC group respectively, without significant difference. The difference in bile duct injuries was mainly caused by eight cases of bile leakage with unknown origin and conservative treatment in the SIC group (five cases from one trial).

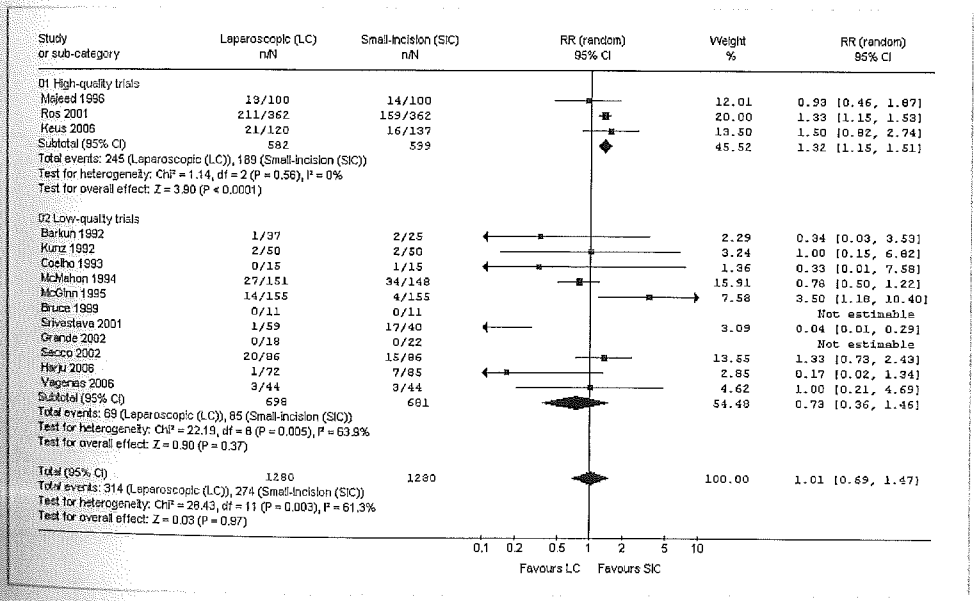

Figure 5: Forrest plot showing individual data and pooled results of total complications including all trials on laparoscopic versus small-incision cholecystectomy.

stay including all trials

2e. Total complications

The total complication proportions including all trials were 24.3% and 21.2% in the laparoscopic and small-incision groups respectively, without significant difference. Total complication proportions in low-bias risk trials [16,19,49] were higher (42.1% and 31.6% respectively) compared with total complications including all randomized trials and significantly lower in the SIC group (Figure 5).

Excluding gallbladder perforations in sensitivity analyses resulted in total complication proportions decreasing to 15.6% and 16.4% respectively. In recalculations including low-bias risk trials, significance disappears both in intra-operative complications (fixed effect: RR: 1.66; 95% CI: 0.96-2.88) and in total complications (fixed effect: RR: 1.07; 95% CI: 0.83-1.37).

A funnel plot raises some suspicion for publication bias considering the absence of small trials favouring the small-incision technique (Figure 6).

3. Symptom relief

Insufficient data on relief of symptoms were available.

Secondary outcome measures

4. Conversions to OC

Conversions were reported in nine trials including 1952 patients. Conversion proporti-

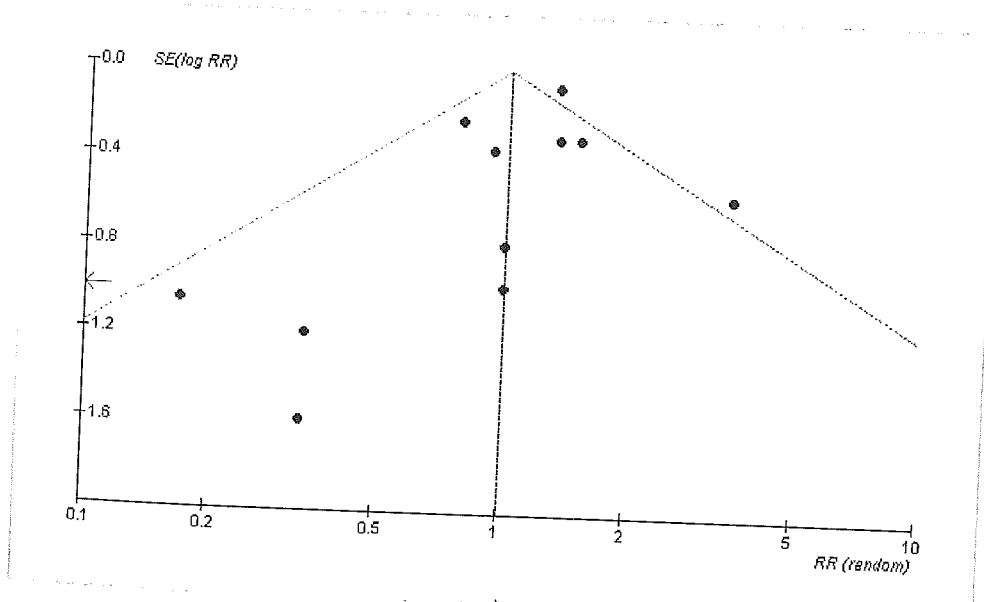

Figure 6: Funnel plots using data of total complications including 95% confidence interval lines. Laparoscopic versus small-incision cholecystectomy.

There is some suspicion of bias considering the absence (in the lower right part) of small trials favouring the small-incision technique.

ons were 12.9% and 15.1%
sions including all trials s
low-bias risk trials show
5. Operative time
Operative time was repc
trials and low-bias risk t
average 16 min) to perfo
6. Hospital stay
Hospital stay was report
pital stay including all tr
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7. Convalescence
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a significant difference.
8. Other secondary outc
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Study or sub-category	N	Laparosc M
01 High-quality trials		
Majeed 1996	100	69
Ros 2001	362	108
Keus 2006	120	71
Subtotal (95% CI)	582	
Test for heterogeneity: Chi² = 9.05, df = 2 (P = 0.01		
Test for overall effect: Z = 4.29 (P < 0.0001)		
02 Low-quality trials		
Barkun 1992	37	85
Kunz 1992	50	102
McMahon 1994	151	71
Srivastava 2001	59	54
Grende 2002	18	42
Secco 2002	86	31
Harju 2006	72	75
Vegenes 2006	44	100
Subtotal (95% CI)	517	
Test for heterogeneity: Chi² = 99.19, df = 7 (P < 0.(		
Test for overall effect: Z = 2.39 (P = 0.02)		
Total (95% CI)	1099	
Test for heterogeneity: Chi² = 139.93, df = 10 (P <		
Test for overall effect: Z = 3.42 (P = 0.0006)		

Figure 7: Forrest plot shov

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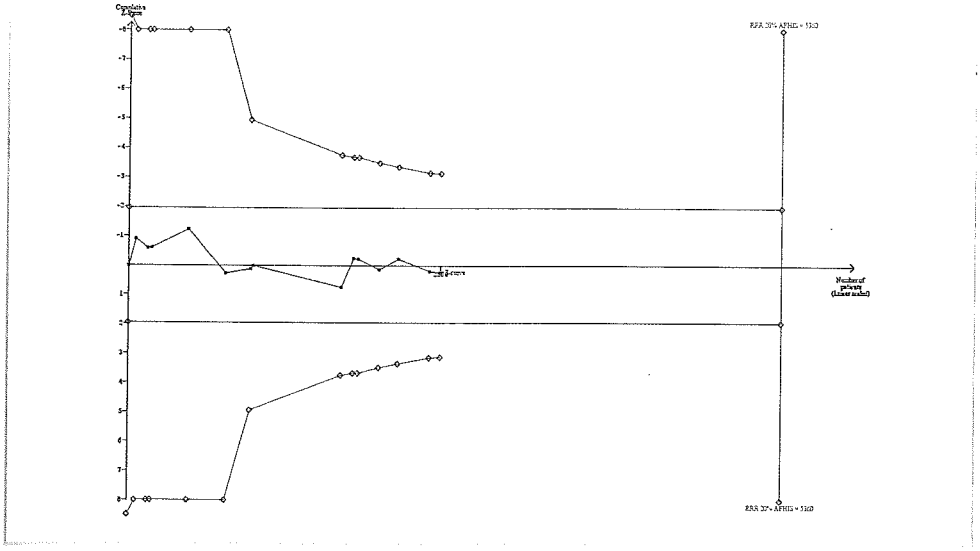

Figure 3: Trial sequential analysis of a priori set heterogeneity adjusted information size (APHIS) and ignoring the Bruce trial [31] as it provides non-detectable information on difference in total complications between laparoscopic and small-incision cholecystectomy.

APHIS = 5354 patients; meta-analysis at 48%; relative risk reduction 20%; control event rate 21.4%.

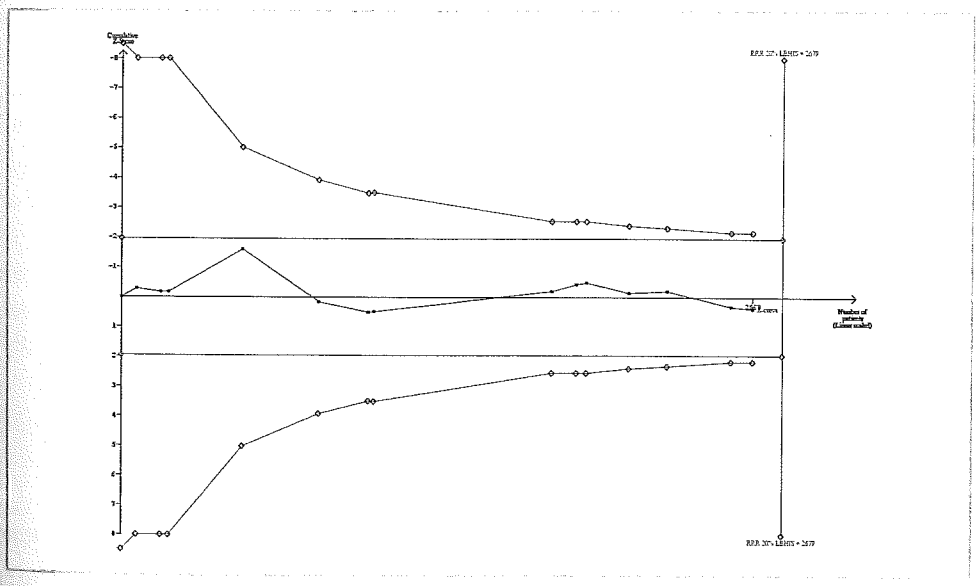

Figure 4: Trial sequential analysis of low risk of bias based heterogeneity adjusted information size (LBHIS) on difference in a composite outcome measure 'serious adverse events' between laparoscopic and small-incision cholecystectomy.

LBHIS = 2679 patients; meta-analysis at 96%; relative risk reduction -31.5%; control event rate 15.7%.

Results of APHIS and LBHIS analyses may differ. APHIS results may originate from clinical a priori guesses of the magnitudes of CERs and RRR, using experiences from related clinical research areas. LBHIS results are based on the specific estimates of these parameters in randomized trials with a low risk of bias performed in the specific research area so far. Large differences between these APHIS and LBHIS results reveal a discrepancy between what may be generally clinically accepted and what is found based on reliable evidence. Both calculations may be wrong: The clinical anticipation of an intervention effect (worthwhile or at hand) may obviously be wrong, although there may also very well be random error in the trials already conducted especially if they have been small. We rely more on the findings of the well-conducted trials with a low risk of bias because clinical "guesstimates" or perceptions represent a lower level of evidence and may very well underestimate true complication rates. However, in the case of only few and small trials with a low risk of bias, we have to consider the IS calculation with realistic anticipations of the intervention effects, as well as, the APHIS TSA.

After mortality, many surgeons usually consider bile duct injuries the second most serious event in cholecystectomy. However, as the event rate is rare, 20,000 randomized patients are needed to reach the required IS for strong evidence regarding this outcome. Therefore, the preference for one of the surgical methods may probably never be answered on the basis of bile duct injuries alone. Likewise, which method has the lowest mortality is a question likely to be impossible to answer in a randomized clinical trial as more than 90,000 patients are needed. Accordingly, it may be more clinically relevant to focus on other "primary" outcome measures.

TSA calculations on severe complications show that the required IS may be within reach. LBHIS TSA show that inclusion of about 582 patients in a new trial with a low risk of bias may be an informative supplement, which may establish definitive evidence in a subsequent meta-analysis. APHIS analysis, however, does not agree that an IS on severe complications is within reach. The difference in both calculations is caused by the differences in both RRR and CER. Although the APHIS conditions (RRR of 20% and CER of 3.9%) seem realistic, trials with a low risk of bias are known for more valid results [5-8]. The question is whether there is a methodological problem in the trials with a low risk of bias or that we are underestimating the CER in the APHIS calculations. Another issue may be that the outcome measure of severe complications ignores mortality, bile duct injuries, and severe intraoperative complications. Although each one of these separately is a rare event, the cumulative total or composite outcome measure of SAE may be a common event. As the two most important outcome measures (i.e., mortality and bile duct injury) could never form a realistic primary research question for a randomized trial, a composite outcome measure is probably the most sensible alternative. We therefore conducted a post hoc analysis, adding all serious complications (mortality,

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CONCLUSION

Our results provide str
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bile duct injuries, severe complications, and severe intraoperative complications) into one composite SAE outcome measure. This composite outcome measure was compiled retrospectively and can therefore only be considered to be hypothesis generating. Our analysis shows a CER of 15.7%, which is large enough to examine a potential clinically relevant difference. The LBHIS required is 2,679 patients based on an RRR of 31.5%, resulting in an additional 119 patients needed. This IS is obtainable with a new trial.

Conducting meta-analyses involves learning from errors in the past related to both systematic errors and random errors. This process of learning should lead to improved methodology in future randomized trials, and bias risk prevention should be optimized. Minimizing random error resulting from repeated testing when meta-analyses are updated is the essential strength of the TSA analysis, which also suggests the required sample size in a future trial [32]. An alternative methodology, simulations based on the posterior distribution of the possible intervention effect derived from a meta-analysis, an open form sample size estimation, may be a more valid method [32]. In contrast, TSA provides a less complicated tool taking heterogeneity and bias risk in previous trials into consideration, although it only provides a closed form estimation of the required IS that does not take the whole posterior distribution into consideration but merely the meta-analytic point estimate reached so far [32].

As a minimum, the four criteria used for methodological quality assessment must be adequate to consider a randomized trial as having a low risk of bias [5,26]. Secondly, primary and secondary outcome measures should be separated clearly to focus on obtaining a valid answer to the initial clinical question [33]. Thirdly, future trials should focus on a well-defined complication and SAE. We have learned that some trials with a high risk of bias, focusing on a distinct research question, found no complications, or did not record complications, causing the zero-event problem [21]. As these trials with a high risk of bias did not focus on complications, they probably simply have not registered what happened. Additionally, proper sample-size considerations must be fulfilled, to obtain correct estimation of precision and power [34].

CONCLUSION

Our results provide strong incentives to conduct a new trial with a low risk of bias focusing on reduction of SAE. This may require a new and sensible composite outcome measure. The required IS for firm conclusions on a low bias-based estimated RRR of 30% and a CER of 16% may be obtainable with a new trial.
In general, we advocate incorporating TSA in future meta-analyses to adjust significance levels, reduce the risk of random errors, and to estimate the required IS to evaluate

whether additional randomized clinical trials are desirable.

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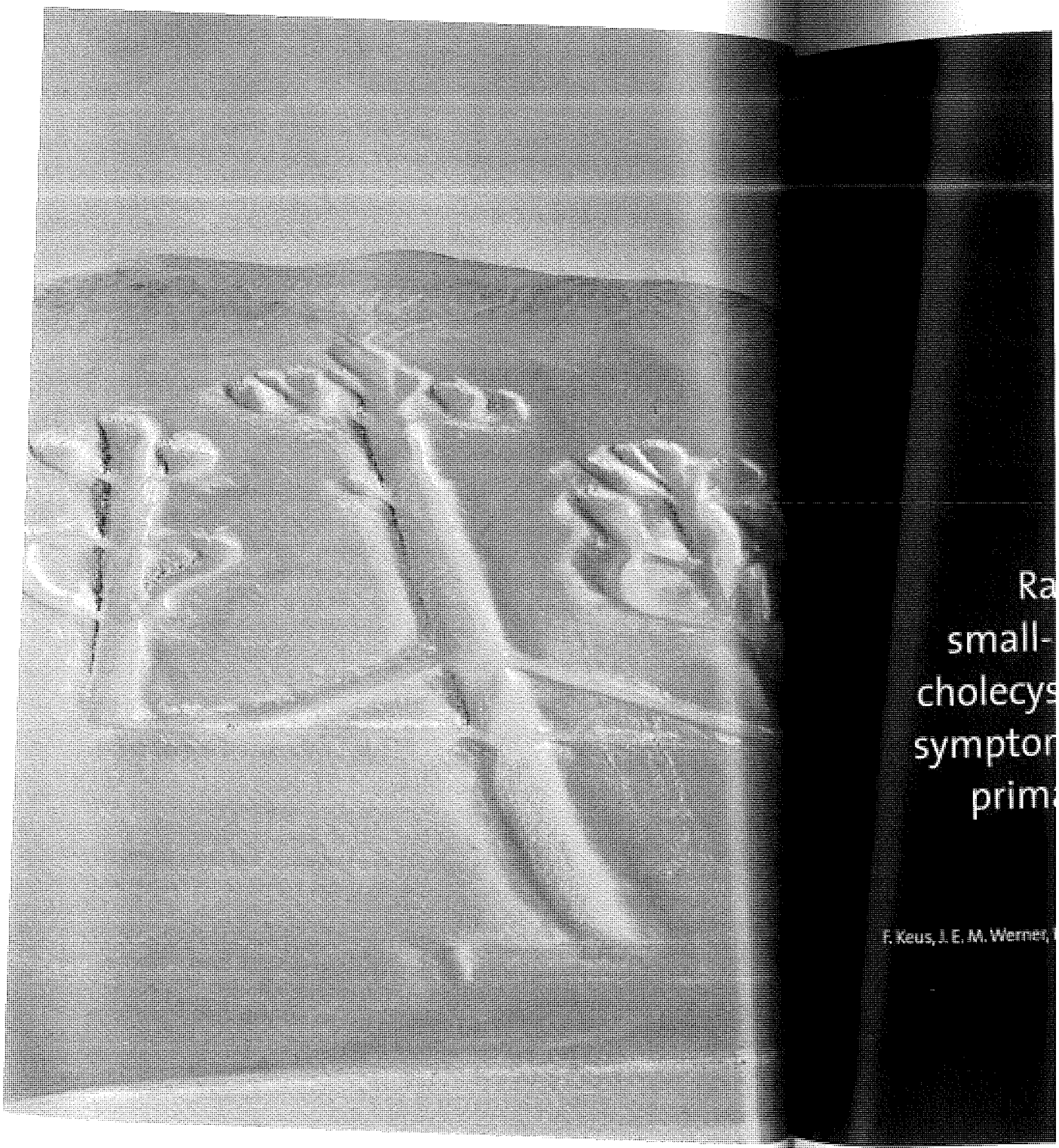
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Randomized clinical trial of small-incision and laparoscopic cholecystectomy in patients with symptomatic cholecystolithiasis - primary and clinical outcomes

F. Keus, J. E. M. Werner, H. G. Gooszen, H. J. M. Oostvogel, C. J. H. M. van Laarhoven

Arch Surg 2008;143(4):371-377

ABSTRACT

Objective
To evaluate the primary and clinical outcomes in laparoscopic and small-incision cholecystectomy.

Design
Blinded randomized single-center trial emphasizing methodologic quality and generalizability.

Setting
General teaching hospital in the Netherlands.

Patients
A total of 257 patients undergoing cholecystectomy for symptomatic cholecystolithiasis.

Interventions
Laparoscopic cholecystectomy and small-incision cholecystectomy, performed mainly by surgical residents.

Main Outcome Measures
Complications and symptom relief were primary outcome measures; conversion rate, operative time, and hospital stay were secondary outcome measures. Feasibility of performing both procedures by residents was evaluated as well.

Results
In the 257 patients, surgical residents performed 105 laparoscopic and 118 small-incision cholecystectomies. There were no significant differences in complications, conversion rates, and hospital stay. Operative time was significantly shorter with the small-incision technique.

Conclusions
No differences in primary clinical outcome measures were found between laparoscopic and small-incision cholecystectomy in this randomized trial with emphasis on methodologic quality and generalizability. The gold standard status of laparoscopic cholecystectomy is questionable.

Trial Registration
isrctn.org Identifier: ISRCTN67485658

INTRODUCTION

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INTRODUCTION

Langenbuch's classic cholecystectomy was the gold standard for treating cholecystolithiasis for more than a century [1]. Shortly after surgeons began making incisions smaller to speed recovery [2-5], laparoscopic cholecystectomy (LC) was introduced and rapidly conquered the world. Its popularity was based on the appeal of the technological innovation as well as enthusiastic marketing by industry, rather than resulting from an evidence-based approach [6,7].

This technique was accepted as the gold standard by consensus in 1993, without a high level of evidence for its superiority [8]. Now, in the modern era of new laparoscopic developments, LC has become the "ideal model" of implementation and justification for a laparoscopic technique. In newer areas for laparoscopic techniques, advantages over previous practice are still under debate. However, true evidence of the superiority of LC to other procedures, such as small-incision cholecystectomy (SIC) and open cholecystectomy (OC), has yet to be assessed.

Whereas the comparison of LC with OC seems to favor LC [9], conflicting results are found in randomized controlled trials comparing LC with SIC [10-21]. Nearly all trials did not discriminate between primary and secondary outcome measures, and only a few trials included surgical residents performing the operations. Differences in methodologic quality of the studies raise doubts about validity, and expert settings bring into question the generalizability.

Therefore, the principal aim of this study, with emphasis on methodologic quality, was to test the generalizability of the comparable outcome of LC and SIC in a general teaching hospital with predominantly surgical residents performing the operations.

METHODS

Our aim was to perform a randomized trial focusing on 3 issues: discrimination between primary and secondary outcome measures, methodologic quality, and generalizability.

Mortality and complication rate are primary outcome measures and the ultimate determining factors in deciding between LC and SIC. On the basis of the available literature, we hypothesized that no major differences in primary outcome measures would be found between LC and SIC. All other outcomes are secondary outcomes (e.g., cost-minimization analysis) and eventually may be deciding factors for choosing one procedure over the other. However, before it is justified to focus on secondary outcomes,

we have to show results of primary outcomes in our study population comparable with those in the literature.

The second issue relates to methodologic quality. Many methods of scoring the intrinsic quality of a randomized trial exist, but none is sufficient. However, only 4 methodologic quality items have proved to be important factors for minimization of bias [22]. We have tried to optimize trial quality in these 4 key domains: generation of the allocation sequence, allocation concealment, blinding, and follow-up.

The third issue relates to generalizability. If a small number of highly experienced surgeons perform all operations in a trial, excellent results might be expected. However, our real world includes surgeons without a high level of experience who also perform cholecystectomies and the training of residents, possibly leading to completely different results. To maximize applicability of the trial results, we needed to include residents performing operations.

This article presents the clinical outcomes of the trial, highlights efforts to minimize bias, and discusses the generalizability of our real-world findings.

Outcome measures

We evaluated the usual baseline characteristics (age, sex, body mass index, and American Society of Anesthesiologists (ASA) score), preoperative biochemistry results, classic diagnostic symptoms, and recovery after complicated gallstone disease. The following outcomes were examined: mortality, complications, symptom relief, operative time, hospital stay, conversion rate, and intraoperative technical aspects. The number of operations performed by residents was recorded as well. Symptom relief was measured by asking all patients whether painful episodes had recurred, as well as whether cholecystectomy had resolved their primary complaint.

Patients

Approval from the Medical Ethics Committee for this single-center trial was obtained in September 2000. Patients were recruited between January 1, 2001, and January 31, 2004. If patients referred to the surgical outpatient clinic met the inclusion criteria and no exclusion criteria were present, written informed consent was obtained. Patients were placed on the waiting list for elective cholecystectomy. If patients wanted to reconsider their participation in the trial, they could be excluded on the day of admission, before randomization.

Inclusion and exclusion criteria

Inclusion criteria were symptomatic cholecystolithiasis (confirmed by ultrasonography)

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in male or female patients, 18 years or older at recruitment, reasonable to good health (ASA score of 1 or 2), no known relevant allergies, and signed informed consent letter.

Exclusion criteria were age younger than 18 years, choledocholithiasis (icterus, acholic feces, and/or bilirubin level of twice the upper limit of normal), cholangitis, known pregnancy, moderate to severe systemic disease (ASA score of 3 or higher), known cirrhosis of the liver, history of abdominal malignant neoplasm, previous upper abdominal surgery (precluding laparoscopic approach), psychiatric disease, or other factor (eg, lack of knowledge of the Dutch language) that might make follow-up or completion of questionnaires unreliable.

Obesity was recorded but was not an exclusion criterion [14]. Recovery after successful endoscopic treatment of choledocholithiasis was not a contraindication. Acute cholecystitis is a different disease with different complication rates, morbidity, and conversion rates and therefore was cause for exclusion.

Randomization

A random-number table was used for generation of the allocation sequence [23], and the allocation concealment was guaranteed by using sealed envelopes (no blocking, no stratification). To eliminate bias caused by preoperative expectations, patients were randomly assigned in the operation room after induction of anaesthesia. A telephone call was placed to the secretarial office and an employee opened an envelope to determine the surgical method. Details of surgery were recorded in a case record form. Otherwise, the procedure was recorded as "trial cholecystectomy". We did not use sealed envelopes for record keeping [17].

Surgical procedures

All consultant surgeons participating in the trial had experience in LC and were trained in SIC in a pilot phase before the trial. After this learning phase, each consultant surgeon was considered equally familiar with the 2 techniques. Operations were supervised by 1 of the consulting surgeons. Our hospital is a training hospital; thus, residents (from second year on) performed most of the operations, which enabled us to test external validity in a teaching hospital.

Although discussions in the literature on intraoperative cholangiography continue, the policy in our hospital was not to perform cholangiography in any patient undergoing elective cholecystectomy. Performing standardized laboratory tests and, on indication, preoperative endoscopic retrograde cholangiopancreatography is the national policy in the Netherlands, based on the broad availability of high-quality endoscopy facilities.

All patients had a standard anesthesia regimen. Premedication, medications for induction and continuation of anesthesia, and respiration during surgery were standardized. Analgesics and medication for nausea were supplied according to a standard scheme.

All patients had nasogastric intubation during the operation that was removed immediately afterward. Operating time was measured from the first skin incision to the last suture placement for both techniques. In case of technical difficulties or for any other reasons, either technique could be converted to OC. No suction drains were left in the subhepatic space at the end of the procedure. Abdominal wall and skin closure were standardized. The wounds were covered with standard wound dressings, with iodine stains applied to the wound dressings to allow blind assessment during clinical stay [14]. We did not use local anaesthetic techniques or intercostal nerve blocks because their application in LC and SIC differs, thereby possibly introducing bias. Identical systemic administration of analgesics in both procedures was used, giving less potential for bias.

Laparoscopic Cholecystectomy

Open introduction was performed in all patients, regardless of previous abdominal surgery. Pneumoperitoneum was created with intra-abdominal pressures up to 12 mm Hg, and 3 trocars were inserted. The dissection of the cystic duct and artery, identifying the Calot triangle, was performed by means of a 3-point "flag" technique [24]. The cystic duct and artery were clipped and transected. After complete dissection, the gallbladder was removed. If conversion to OC was necessary, the reasons for conversion were recorded.

Small-Incision Cholecystectomy

In accordance with the literature, a cutoff point of 8 cm was used to differentiate between SIC and OC [11-21]. As part of a separate research question, all patients underwent preoperative ultrasound for location of the gallbladder. We used the craniocaudal position of the mark for incision. The incision was placed over the musculus rectus abdominis. Only standard instruments were used, with no special equipment. Access to the peritoneum was obtained by a muscle splitting (and not transection) technique (comparable to open appendectomy). The gallbladder was dissected by a "fundus-first" technique. If necessary, the gallbladder was punctured to remove its liquid contents. The cystic duct and artery were ligated and the gallbladder was removed. Posterior and anterior fascias were closed separately. After wound closure, the length of the incision was measured; if it exceeded 8 cm, the operation was considered a conversion to OC. The reasons for conversions were recorded.

Postoperative protocol

Early oral intake and mobilization were encouraged. Patients left the hospital as soon

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Analysis and sample size

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as they were able to do so. Although ambulatory cholecystectomy has been proved feasible, it was not practiced in our hospital [25]. Hospital stay was defined as the number of postoperative nights in the hospital. Shortly before discharge, wound dressings were removed for wound inspection. Follow-up took place after 2 weeks, 6 weeks, and 3 months. For logistic reasons, we were not able to blind the surgeon at follow-up. Patients were encouraged to resume work and normal daily activity as soon as they felt able to do so.

Analysis and sample size

Assuming no differences in primary outcome measures, sample size calculation was based on differences of costs. For this purpose, the direct costs of the first 50 patients in the trial were calculated to estimate the likely range of differences in costs and their standard deviations. On this basis, we estimated that 120 patients per group would be needed to detect a difference of 10% in direct costs using an α of 0.05 and a β of 0.9. Although such analysis was not the purpose of this trial, a difference of 10% in complications would have been possible to detect with this sample size. Before the reporting of costs would be allowed, the data set of the trial had to be validated in regard to the primary outcome measures (complications and symptom relief). After primary outcomes comparable to those in the literature were demonstrated, it would be justified to report secondary outcomes such as costs. No interim analysis was planned, but the monitoring committee could stop the trial if a substantial difference in complications occurred.

All data were stored in a case record form and subsequently transferred to an Access database. Double data entry was performed to prevent typing errors. Data were subsequently read into SPSS 11.0 (SPSS Inc, Chicago, Illinois) for statistical analysis.

Statistics

Comparisons were made on an intention-to-treat basis [26]. Calculations were made with SPSS 11.0. The χ^2 test was used for dichotomous outcomes. For all continuous data, we present our results both as medians with ranges and as means with standard deviations to facilitate their interpretation.

The normality of the data was checked by means of the Kolmogorov-Smirnov test. In case of deviations from normality, data were transformed to normality [27]. The Levene test was used for checking the equality of variances. When the condition of normality and equal variances was met, the independent samples t test was used for independent data. When equality of variances was absent or normality could not be reached with transformation, the nonparametric Mann-Whitney test was used.

RESULTS

All trial patients were operated on between January 1, 2001, and March 31, 2004. Initially, 366 patients fulfilled the inclusion criteria and agreed to be included in the trial. A total of 102 patients were not randomized for a variety of reasons (Figure 1) [28]. After 264 patients were randomly assigned, another 7 patients were excluded for the following reasons: unwillingness to participate further (2 patients), intraoperative suspicion of malignant neoplasm (2 patients), transfer to another ward not participating in the trial (1 patient), participation in 2 trials (not in line with the Helsinki declaration)

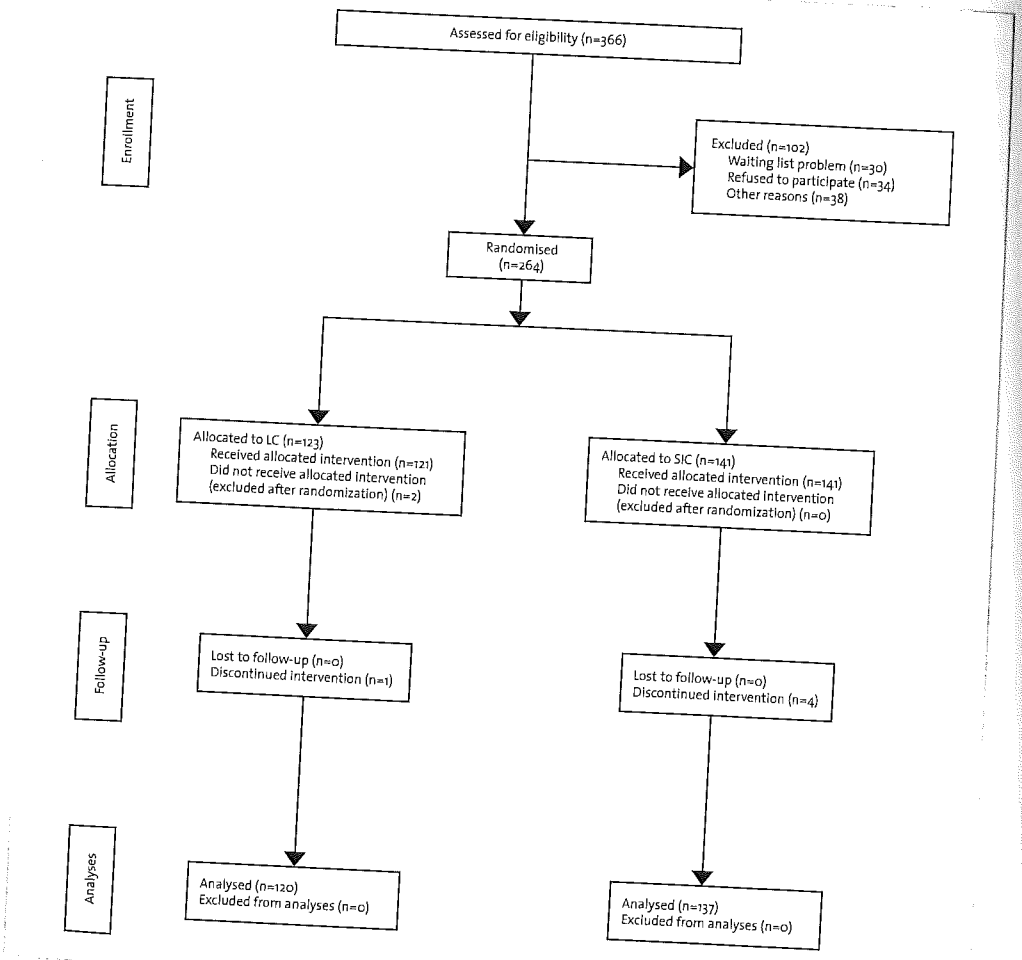

Figure 1: Revised consort statement diagram showing the flow of participants through each stage of the randomised trial (35).

LC: laparoscopic cholecystectomy; SIC: small-incision cholecystectomy.

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Abbreviations: ASA, Ameri
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(1 patient), and insufficient knowledge of the Dutch language (1 patient). A total of 257 patients were left for analysis (Figure 1).

Baseline characteristics

The 2 groups did not differ with regard to age, sex, body mass index, and ASA classification (Table 1) [29]. We evaluated the following classic diagnostic symptoms of cholecystolithiasis in both groups [30]: severe pain, episodic pain, epigastric pain, pain in the right upper quadrant, pain radiating to the back, pain lasting 1 to 5 hours, awakening at night, and the Murphy sign. There were no significant differences in the presence and the duration of these symptoms. The numbers of patients presenting with complicated gallstone disease and operated on in a later stage were also equally distributed (Table 1). Preoperative blood analysis consisting of erythrocyte sedimentation rate, white blood cell count, levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, and bilirubin showed no significant differences between groups.

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	p-value
Sex, No. (%)			0.46
Male	31 (25.8%)	30 (21.9%)	
Female	89 (74.2%)	107 (78.1%)	
Age, y			
mean (SD)	48.4 (14.1)	48.5 (14.0)	0.97
median (range)	49 (17-77)	48 (18-80)	
BMI			
mean (SD)	27.5 (4.8)	27.9 (4.6)	0.50
median (range)	26.8 (18.5-45.9)	27,2 (18.0-43.3)	
ASA (%)			0.86
I	81 (67.5%)	91 (66.4%)	
II	39 (32.5%)	46 (33.6%)	
Complicated gall stone disease, No	18	18	0.67
Acute cholecystitis	1	0	0.28
Cholangitis	3	3	0.87
Biliary pancreatitis	4	8	0.34
Bile duct stone and icterus	10	7	0.30
ERCP before cholecystectomy, No	12	13	0.89

Table 1: Patient characteristics.

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ERCP, endoscopic retrograde cholangiopancreatography.

Operative results

Results are presented including data from converted operations (intention-to-treat) unless otherwise stated.

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Statistical analysis
Complications, No.	21	16	
intra-operative	5	3	p=0.36
postoperative	16	13	p=0.33
Conversion rate, No. (%)	14 (11.7%)	22 (16.1%)	p=0.31
Failure of symptom relief, No. (%)	11 (9.2%)	14 (10.2%)	p=0.78
Operative time, min			
mean (SD)	71.9 (25.8)	60.4 (18.3)	p<0.001
median (range)	68.5 (26-215)	60.0 (29-105)	
Operative team, No. (%)			
surgeon-resident	15 (12.5%)	19 (13.9%)	p=0.52
resident-surgeon	84 (70.0%)	100 (73.0%)	p=0.560
resident-resident	21 (17.5%)	18 (13.1%)	p=0.33
Incision length, mm[a]			
mean (SD)	76.1 (33.8)	76.0 (24.0)	p=0.2
median (range)	65 (40-200)	66 (49-165)	
Hospital stay, postoperative nights			
mean (SD)	2.4 (4.6)	3.1 (12.4)	p=0.56
median (range)	1 (1 - 36)	2 (1 - 144)	
mean (SD) excluding 1 extreme value	2.1 (3.4)	2.4 (2.4)	p=0.88
Number of patients with:			
1 night stay postoperative	67 (55.8%)	62 (45.3%)	p=0.09
2 nights stay postoperative	38 (31.7%)	56 (40.9%)	p=0.13
Follow-up:			
2 weeks	112 (93.3%)	133 (97.1%)	p=0.16
6 weeks	106 (88.3%)	130 (94,9%)	p=0.06
3 months	96 (80.0%)	111 (81.0%)	p=0.24
Employed (n)	50	51	
Return to work (weeks):			
mean (SD)	4.1 (2.3)	3.7 (2.0)	p=0.3
median (range)	4 (1-12)	3 (0.5-12)	

Table 2: Comparison of operative results.

[a]incision length was measured in 95 patients (12 conversions) in the laparoscopic group and 134 patients (20 conversions) in the small-incision group.

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Complications

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Obesity (gallbladder tear,	
Inflammation (cholecystit	
Uncontrollable bleeding f	
Common bile duct injury (conversion and choledoc	
Inadequate positioning c over liver (insufficient vie	
Total	

Among intraoperative factors, we found more adhesions (χ^2=9.15, p=0.002) and intraoperative bile leakage (by gallbladder perforation) (χ^2=10.26, p=0.001) in the LC group. Correspondingly, the skin was left open for secondary wound healing more often in the LC group (χ^2=31.69, p<0.001). Intraoperative stone loss, presence of inflammation, and identification of the cystic duct and the common bile duct were not statistically different between the 2 groups. The cystic artery (p=0.005) and Calot triangle (p<0.001) were identified more frequently in the LC group, and in the SIC group a combined ligation of the cystic duct and artery was performed more frequently (p<0.001).

Surgical residents performed 105 LCs (87.5%) and 118 SICs (86.1%). Operative time was shorter for SIC (60 vs 72 minutes; U=6013.0; p<0.001) (Table 2). Conversion rates were similar, with similar distribution of reasons for conversion (Table 3). Total incision length of scars, measured in 229 patients, appeared to be not statistically different between the LC and SIC groups.

Complications

There were no deaths in the trial. There were 5 intraoperative complications in the LC group and 3 in the SIC group (Table 4). Most importantly, 1 common bile duct injury occurred in each group (treated by T-drainage and hepaticojejunostomy). Considering postoperative complications, we did not find a difference in the number or severity between the 2 groups.

Laparoscopic Cholecystectomy		Small-Incision Cholecystectomy	
Because of adhesions	5	Insufficient view	9
Unclear anatomy / no overview	3	Cholecystitis	3
Obesity (gallbladder tear, technical problems)	2	Gallbladder to deep under rib cage (insufficient view)	3
Inflammation (cholecystitis and empyema)	1	Bleeding (from cystic artery)	3
Uncontrollable bleeding from cystic artery	1	No progress after 50 minutes	1
Common bile duct injury (conversion and choledocho-jejunostomie)	1	Hepatic duct injury (T-drainage)	1
Inadequate positioning of gallbladder over liver (insufficient view)	1	Stone was impacted in cystic duct, impossible to remove	1
		By accident larger incision (10cm)	1
Total	14	Total	22

Table 3: Reasons for conversions.

The numbers of complications in the "resident-resident" operative team subgroups were compared in an exploratory subgroup analysis. These numbers (3 and 4 in the LC

Laparoscopic Cholecystectomy (total)	21	Small-Incision Cholecystectomy (total)	16
Intraoperative complications		Intraoperative complications	
Asystole	1	Cardiac ischemia, no elevated enzymes	1
Common bile duct (CBD) injury, eventually hepatico-jejunostomy, complicated prolonged ICU stay, stenosis bile duct.	1	CBD injury, conversion, T-drain, ERCP and papillotomy for CBD stone	1
Bleeding requiring conversion (and transfusion)	1	Hepatic parenchyma rupture, conservative treatment (transfusion)	1
Bowel injury at introduction (sutured)	1		
Cerebrovascular accident at recovery	1		
Total intraoperative	5	Total intraoperative	3
Postoperative complications		Postoperative complications	
Pneumonia	1	Cystic duct leakage (ERCP + stent)	1
Cerebrovascular accident (6 weeks postoperative)	1	CBD injury, multiple relaparotomies and ICU stay	1
Intra-abdominal fluid collection (haematoma); icterus (ERCP: no stones, complicated by bleeding)	1	CBD stone (ERCP) and abscess intra-abdominal (ultrasound drainage)	1
Pancreatitis (conservative treatment)	1	CBD stone with mild pancreatitis (ERCP)	1
Intra-abdominal abscess (re-laparoscopy)	1	Urinary tract infection (antibiotics)	1
Epididimitis (operation by urologist)	1	Urinary retention	1
Phlebitis	3	Wound infection	3
Urinary tract infection (urologist)	1	Wound dehiscence (no macroscopic infection)	4
Wound infection: umbilical	3		
Wound haematoma	2		
Wound infection: subxiphoidal	1		
Total postoperative	16	Total postoperative	13

Table 4: Intraoperative and postoperative complications.

ERCP: endoscopic retrograde cholangiopancreatography.; ICU: intensive care unit.

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and SIC groups, respectively) were not different from complication rates in operative teams that included a surgeon.

Postoperative complaints

The follow-up rate between the groups was not statistically different. Follow-up in the LC and SIC groups, respectively, was 88.3% and 94.9% at 6 weeks, 80.0% and 81.0% at 3 months, and all patients showed up at either their 6-week or their 3-month follow-up appointment. All patients who did not show up at their 2-week or 6-week follow-up appointment appeared not to have any problems at their next scheduled follow-up appointment.

Whether symptom relief was achieved and whether symptoms had recurred was ambiguously reported by some patients. With unclear cases included, it appeared that 9.2% and 10.2% of patients in the LC and SIC groups, respectively, experienced failure of symptom relief (Table 2).

Postoperative complaints at follow-up were evaluated and appeared comparable between the LC and SIC groups, including dietary complaints (26 vs 30 patients; p=0.96), diarrhea (17 vs 15; p=0.44), fatigue (13 vs 6; p=0.049), and complaints suggesting the presence of common bile duct stones (6 vs 9; p=0.59). There was also no statistical difference in the number of patients undergoing endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreaticography postoperatively (2 vs 5; p=0.24).

COMMENT

There were no differences in baseline characteristics between the 2 groups of patients, suggesting an effective randomization process. We found no significant differences in primary and secondary outcome measures between LC and SIC: complication rate (both intraoperatively and postoperatively), symptom relief, conversion rate, and hospital stay. Operative time was shorter in the SIC group. The results of this study compare well with those in the literature but add to it in terms of methodologic quality and real-world general teaching hospital setting.

Results of previous randomized controlled trials have been contradictory. Trials in the literature together include more than 2000 patients. Most trials found no difference in complication rates between LC and SIC [10,12,14,16], whereas in 2 trials complication rates were lower with SIC [15,17]. However, complication rates vary substantially between the different trials, without unambiguously showing lower complication rates in trials

with expert settings. Differences in intrinsic validity probably also play a role in varying complication rates.

Most trials found a shorter operative time for SIC [14,15,17], whereas 2 other trials did not [10,12]. Results for hospital stay [10,12-17,19,20] and convalescence [10,14,16,17] are conflicting as well. Overall, most authors conclude that there is no difference between the 2 procedures [12-15,17]. Considering these conflicting but numerous data, pooled estimates by meta-analysis are needed to derive strong conclusions [31].

Minimizing bias gives considerable strength to results. Although it is not possible to be sure that all patients really were blinded to their treatment, expectations of ward personnel influencing postoperative recovery probably is a much more important factor in convalescence.

Generalizability includes extrapolation of study results to other patient categories or other surgical units. We believe that extrapolation of these results (surgery performed largely by residents) to other surgical units is possible without increased risk. However, extrapolation to other patient categories (ie, those with ASA scores of 3 or 4, or patients with cholecystitis) is dangerous because it uses assumptions that may not hold true. Additional research exploring the appropriateness of extrapolation of these results to other patient categories is necessary. Unlike the evidence in expert studies [14], we have shown the feasibility of SIC and LC in a general teaching hospital with mainly surgical trainees (86% and 88%) performing the operations. We believe that this reflects a real-world situation and adds to the generalizability.

In a short training phase, surgeons were taught the SIC technique. After this introductory phase, all participating surgeons were considered equally familiar with both techniques. In reality, they probably were more experienced with LC. Explorative analysis of this theoretical difference in experience by comparing early with later results did not show any difference in outcome.

Opportunities to learn the OC technique are few because conversion rates are too low to provide enough numbers. Small-incision cholecystectomy with extended incision if necessary appears to be a valuable alternative. An advantage of this strategy is that it familiarizes residents with the open approach and precludes the performance of an unknown procedure. It seems useful to add the small-incision technique to the repertoire of the general surgeon.

At the time the trial started, general policy in the Netherlands (and in our hospital) was not to perform intraoperative cholangiography. Discussions on selective use vs standard

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CONCLUSIONS

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or no cholangiography continue. Recent research shows the benefit of intraoperative cholangiography [32]. Possibly this policy should be reconsidered on the basis of these findings, both in our hospital and on a national level. This issue is currently being studied by a national committee on guideline development of diagnosis and treatment of gallstones.

Hospital stay in this study might be considered long compared with everyday practice. Although ambulatory cholecystectomy has proved feasible with both the laparoscopic and small-incision techniques [33,34], it was not the policy in this hospital at the start of the trial. Both cultural factors and differences in expectations of patients, as well as arrangements with insurance companies at that time, were responsible. In addition, it should be remembered that hospital stay is a surrogate marker for recovery and that it is influenced by many factors, some unknown.

Evidence of superiority of LC to SIC is lacking, and conflicting data arise from the existing randomized trials [10-21]. It is remarkable, however, that the acceptance of LC was extremely rapid: within 3 years, from 1989 to 1992, the rate of laparoscopy for cholecystectomy in the United States changed from 0% to 80% [35]. Moreover, it became the treatment of choice by consensus of the National Institutes of Health in 1993. This is especially remarkable because there had been no possibility of acquiring an adequate level of evidence within this very short period [8]. Analysis afterward showed that access to positive information, more favorable adoption costs–related conditions, and the role of the "early adopters" had been most important in this process [6].

Whereas in the 1980s, the "age of optimism", technical innovation dominated decision making in medical science, currently health technology assessments and cost-effectiveness analyses of treatments play a dominant role [7]. It was, therefore, interesting to compare the presumed clinical superiority of LC, the ideal example of laparoscopic innovation, with more basic minimally invasive techniques such as SIC. With budget restrictions in mind, it is worthwhile looking at other factors that may play a role in future decisions on laparoscopic surgery.

CONCLUSIONS

This randomized controlled trial with emphasis on methodologic quality and generalizability shows no benefit in clinical outcome measures of LC compared with SIC. The question arises of which other measures do differ to persuade us of superiority of one minimally invasive technique over the other. In extending these conclusions to the broad discussion on laparoscopic gastrointestinal surgery, should we be looking for other out-

come measures, such as cost-effectiveness? Or should we look for other factors such as fast-track recovery programs that seem to outweigh some of the effects of laparoscopic surgery, rendering the surgical approach of secondary interest?

Surgical decision making should be evidence based. A systematic review of all randomized controlled trials on this topic should derive the highest possible evidence and surgeons should dare to act accordingly.

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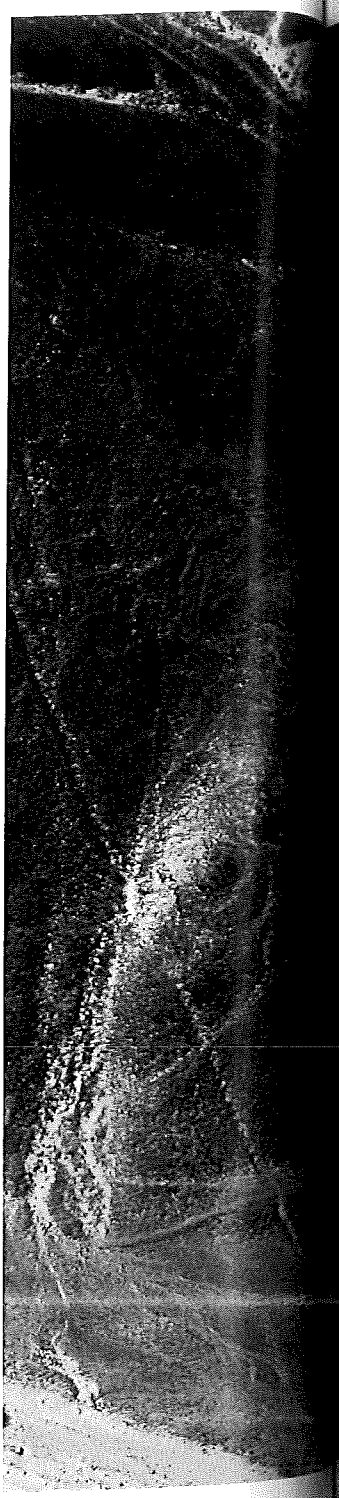

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Anaesthesiological considerations in small-incision and laparoscopic cholecystectomy in symptomatic cholecystolithiasis: implications for pulmonary function. A randomized clinical trial

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ABSTRACT

Background

Upper abdominal surgery, including laparoscopic cholecystectomy (LC), is associated with post-operative pulmonary dysfunction. LC has, by consensus, become the treatment of choice for symptomatic cholecystolithiasis. Small-incision cholecystectomy (SIC), a procedure that does not require a pneumoperitoneum, threatens to be lost to clinical practice, even though there is evidence of equality. We hypothesized that the SIC technique should be equal, and might even be superior, to LC when considering post-operative pulmonary function because of the short incision length.

Methods

A single-centre randomized clinical trial was performed including patients scheduled for elective cholecystectomy. Pulmonary flow-volume curves were measured pre-operatively, post-operatively, and at follow-up. Blood gas analyses were measured pre-operatively, in the recovery phase, and on postoperative day 1. Anaesthesia, analgesics, and peri-operative care were standardized by protocol. Post-operatively, patients and caregivers were blind to the procedure.

Results

Two hundred and fifty-seven patients were analysed. There was one pulmonary complication (pneumonia) in the LC group. In both groups, similar reductions of approximately 20% in pulmonary function parameters occurred, with complete recovery to pre-operative values. Patients in the SIC group consumed more analgesia when compared with the LC group, without any impact on blood gas analysis. Patients converted to a conventional open technique showed significant differences in six of the eight parameters in pulmonary function tests.

Conclusion

When evaluated with strict methodology and standardization of care, no clinically relevant differences were found between SIC and LC with regard to pulmonary function. Our results suggest that the popularity of the laparoscopic technique cannot be attributed to pulmonary preservation.

BACKGROUND

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BACKGROUND

Subsequent to its publication in 1882 [1], open cholecystectomy (OC) was considered as a safe standard for cholecystectomy for about 100 years, although this technique was associated with relevant anaesthesiological and pulmonary risks. A decrease in the length of the incision, known as small-incision cholecystectomy (SIC), with a concomitant decrease in post-operative morbidity, was reported as early as the mid-1970s [2]. However, before SIC could find general acceptance, laparoscopic cholecystectomy (LC) was introduced in the late 1980s [3]. The LC procedure gained rapid and immense popularity [4], and became the surgical treatment of choice, even though its superiority has not been demonstrated [5].

Many important factors have been implicated in the pulmonary compromise seen after upper abdominal surgery, as well as in the cardiovascular risks. These factors include the site and size of the incision, post-operative pain, and reflex inhibition of diaphragmatic function [6]. Compared with the traditional open technique, the cardiopulmonary changes, particularly heart rate and arterial blood pressure changes, following LC have been suggested to be of a lesser order. This combination has convinced many anaesthesiologists that patient care is improved using the laparoscopic technique [7]. However, LC involves adaptation of anaesthesia techniques, as well as patient selection. Pneumoperitoneum has its own procedure-related effects. Intra-abdominal pressure has been associated with extensive elevation of the diaphragm and increased intrathoracic as well as intracranial pressure. Depression of haemodynamic functions, particularly in cardiac output, may place patients with congestive heart failure at increased risk, whereas those with pulmonary disease are exposed to increases in V_A/Q mismatch, increased ventilation requirements, and the risk of pneumothorax peri-operatively [8-10].

A loss of functional residual capacity (FRC), as well as the diaphragmatic contribution to tidal volume, has been suggested to be principally a result of pain-induced shallow breathing (splinting) [6,11,12]. However, only partial restoration of pulmonary function is demonstrated when analgesia is adequately applied [13], implicating other factors and invalidating the eloquent argument that a laparoscopic technique is justified for pulmonary reasons. Controlled prospective studies between LC and SIC, in which anaesthesia considerations and pulmonary function are the principal outcomes, have not been reported.

With improvements in the insight into differences between splinting and pulmonary dysfunction, leading to adaptations in peri-operative management and pain control methods, such as patient-controlled analgesia (PCA), the suggestion that the laparoscopic technique should be preferred over the small-incision technique can be questioned.

Pulmonary function differences between LC and SIC have been studied in only a few, technically oriented, randomized trials, which have reported inconsistent outcomes [14-20], involve small numbers of patients [14,18,19], and seem to incorporate some important methodological shortcomings [15,19,20].

As the literature is ambiguous, we decided to perform a large single-centre randomized trial. The aim was to evaluate pulmonary function in patients randomized between LC and SIC by measuring flow-volume curves and blood gases in a blind fashion.

METHODS

Ethics committee approval for this trial was obtained from St. Elisabeth Hospital (Tilburg, The Netherlands) in September 2000. Patients were recruited from January 2001 to January 2004. Patients referred to our surgical outpatient clinic with symptomatic cholecystolithiasis were eligible for inclusion in the trial. All patients had symptomatic gallstones confirmed by ultrasonography. If patients met the inclusion criteria, and no exclusion criteria were present, written informed consent was obtained and patients were consecutively scheduled for elective cholecystectomy.

Endpoints and outcome

The principal outcome measures of this paper are pulmonary function and related aspects. For the study as a whole, multiple outcomes were evaluated, including mortality, complications, health status, cosmetic results, and cost analyses [21]. Although not the primary focus of this paper, complication rates [22] are mentioned to allow for comparison.

Inclusion and exclusion criteria

The inclusion criteria were as follows: male or female patients with symptomatic cholecystolithiasis; age of 18 years or older at recruitment; American Society of Anesthesiologists (ASA) classification I or II [23]; no known relevant allergies; a signed informed consent letter. Obesity was not considered as an exclusion criterion.

The exclusion criteria were as follows: age younger than 18 years; choledocholithiasis (icterus, acholic stools, and bilirubin of twice normal range); cholangitis; known pregnancy; ASA class III and higher; known cirrhosis of the liver; history of abdominal malignancy; previous surgery which would exclude a laparoscopic procedure; psychiatric disease or other reasons (e.g. inadequate Dutch language skills) making follow-up or answers on the questionnaires unreliable.

Patients suffering from acute cholecystitis could only be included after a cooling down

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period of 3 months and normalization of biochemistry. Inclusion of patients with choledocholithiasis after successful endoscopic treatment was also allowed when liver enzymes had normalized.

Randomization and blinding

A random number table was used to generate the allocation sequence, with allocation concealment guaranteed by sealed envelopes [24]. To further eliminate bias, patients were randomized in the operation theatre after induction of anaesthesia by calling the secretary who opened an envelope. All patient data were recorded in a case record form, with the procedure reported as 'trial cholecystectomy' [25]. Wounds and port sites were dressed with identical opaque dressings, stained using iodine, regardless of the surgical procedure performed, to allow blinding for patients, nurses, technicians, and physicians during the post-operative period [26]. The type of operation was revealed on the morning of discharge.

Standardized anaesthesia protocol

To avoid bias during the peri-operative recovery, all patients were subjected to a standard anaesthesia regime. Any violations to this regime were recorded. Standard pre-medication included diazepam (Valium) (5 mg orally when <50 kg or >65 years; otherwise 10 mg orally) and atropine (0.25 mg intramuscularly when <50 kg or >65 years; otherwise 0.5 mg intramuscularly), given 60 minutes before the operation.

At induction, all patients received 2 g cefazoline (Kefzol) intravenously. The patients were preoxygenated with 100% O_2 for 3 min. Anaesthesia was induced with thiopental (Pentothal) (5 mg/kg intravenous bolus in 2 min), sufentanil (Sufenta) (0.1 µg/kg intravenous bolus; +0.05 µg/kg bolus when indicated) and rocuronium bromide (Esmeron) (0.6 mg/kg intravenously). Routine use of neostigmine with atropine (Prostigmin) was avoided, except where neuromuscular monitoring (TOF-guard) showed a train-of-four of less than four twitches, with fade of more than 30%. Intubation took place with an endotracheal tube (size 8 or 9), and respiration was initiated with a tidal volume of 8 ml/kg, respiration rate of 12 breaths/min, positive endexpiratory pressure (PEEP) of 5 cmH_2O and an end-tidal CO_2 target of 4.0-4.7 kPa. This has been documented to achieve a P_aCO_2 of end-tidal CO_2 + 0.8 kPa. Average intra-abdominal pressures during LC vary between 10 and 14 mmHg in our hospital, with the maximum pressure limited to 14 mmHg. If needed to maintain normocapnia, tidal volume increases of 1-ml/kg steps were alternated with increasing ventilation frequency. Particularly during the termination of anaesthesia, no CO_2 over 7.3 kPa was accepted.

Respiration was continued with O_2 at 40% in air and sevoflurane (Ultane) at 1 MAC (minimal alveolar concentration), corrected for age. Sufentanil (Sufenta) (0.05 µg/kg

intravenous bolus) was given if there was a change in blood pressure or heart rate from the pre-operative value of more than 30%. Rocuronium bromide (Esmeron) (0.125 mg/kg intravenous bolus) was given when indicated by a change in respiratory pressure or when requested by the surgeon.

After induction, patients were positioned on the operation table at an anti-Trendelenburg position of 20°. In accordance with good clinical practice, values of ≤20% of baseline were maintained. Patients left the operation room pain-free and without nausea. Patients were moved directly to recovery, where they were given 2 l/min oxygen via a nasal cannula. This was up through the arterial blood gas evaluation. They were attached to the standard, non-invasive monitoring up through the moment of the arterial blood gas evaluation. Nursing staff (one nurse to three patients) followed all patients. Criteria for discharge from recovery were checked using the Aldrete score, and were confirmed by the anaesthesiologist responsible.

Analgesics in the post-operative period were supplied according to a standard scheme. On arrival in recovery, 1 g paracetamol (suppository) was given, followed, as needed, by diclofenac (Voltaren) (75 mg intravenously to a maximum of 3 times a day). In the recovery room, pethidine (Demerol) 0.5 mg/kg was given once if requested. Morphine 10 mg intravenously, followed by boluses of 5 mg intravenously, to a maximum of 4 times a day, was given for further pain relief. Paracetamol (1 g suppository) was given every 6 h for the first 48 h post-operatively.

Medication for nausea consisted of metoclopramide (Primperan) (10 mg intravenously in 5 min), haloperidol (Haldol) (2.5 mg; and, when indicated, 2.5 mg extra) and ondansetron (Zofran) (4 mg intravenously), if necessary.

The supply of analgesics for pain minimization was objectified using a visual analogue scale (VAS) ruler. Both pain and nausea scores were measured by the VAS ruler in the recovery room every 10 min for 60 min, and were noted in the case record form. When the score was >4, the next step in medication was taken. Patients stayed in the recovery room for at least 1 h to guarantee adequate pain control. Patients were sent to the ward pain-free and without nausea. On the ward, the pain and nausea scores (scored every 2 h) and the standard medication regime were continued until patients had a score of ≤4 for at least 12 h.

Surgical techniques

For LC, an open introduction was performed in all patients, regardless of previous abdominal surgery. Pneumoperitoneum was created with intraabdominal pressures of up to 12 mmHg. Three trocars were inserted. The dissection of the cystic duct and artery,

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and identification of Calot's triangle were performed using a three-point 'flag' technique [27]. The cystic duct and artery were clipped and transected. After complete dissection, the gallbladder was removed.

The SIC approach involved a transverse incision of no more than 8 cm over the right musculus rectus abdominis [19]. Only standard surgical instruments were used, as well as regular operation room (OR) lights; no special equipment was employed. Access to the peritoneum was obtained by a muscle splitting technique, as opposed to transection, comparable with the technique used in an open appendectomy. The gallbladder was dissected 'fundus first'. If necessary, the gallbladder was punctured to remove its liquid contents. The cystic duct and artery were ligated and the gallbladder was removed. Posterior and anterior fascias were closed separately. After wound closure, the length of the incision was measured. If the length of the incision exceeded 8 cm, the operation was considered as a conversion to OC.

A learning curve for the SIC technique was allowed prior to the study. As all surgeons had extensive experience with OC, after approximately five procedures each, adequate experience in the procedure was deemed to be present.

Pulmonary function tests

Pulmonary function tests were performed immediately pre-operatively, on the first post-operative day, and at the 6-week outpatient check-up. During the tests, the best flow-volume curve of three attempts was taken for analysis. The maximal vital capacity (VC_{max}), forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), maximum expiratory flow when 25%, 50%, and 75% of the FVC has been exhaled (FEF_{25}, FEF_{50}, FEF_{75}), peak expiratory flow (PEF), and forced inspiratory volume in 1 s (FIV_1) were documented. The FEF values have been suggested to be particularly sensitive for detecting peri-operative function changes [28]. The pulmonary function tests were performed in our respiratory laboratory using Jaeger-masterscreen PFT (Viasys, Hoechberg, Germany).

Arterial blood gas analyses were performed three times. The pre-operative and 24-h post-operative samples were taken under room air conditions; the sample during recovery was taken at a fraction of inspired oxygen (F_iO_2) of 34% (2 l flow via nasal cannula) at 1 h after detubation. From these arterial blood samples, oxygen saturation, acidity (pH), partial oxygen pressure (pO_2), partial carbon dioxide pressure (pCO_2), base excess, and bicarbonate concentration (HCO_3) were determined.

Post-operative protocol

Early oral intake (within 4 h) and mobilization were encouraged, and patients were eligible for discharge as soon as they felt well enough. Standard practice was to keep all

patients at least one night; some, because of limitations in their home environment, for example, stayed longer. In effect, many patients elected to leave the hospital on the afternoon of the first or second post-operative day. Shortly before discharge, wound dressings were removed for wound inspection, and the type of operation was revealed. Follow-up took place after 2 weeks, 6 weeks, and 3 months, according to a standardized scheme.

Sample size

To avoid post hoc analyses, multiple outcome measures were defined for evaluation in this trial. Analysis of cost aspects was used to determine the power and sample size of the study as a whole. On this basis, we estimated that 120 patients per group would be needed to detect a difference of 10% in direct costs with $\alpha = 0.05$ and $b = 0.9$.

No interim analysis was planned, but a monitoring committee was tasked to terminate inclusion if a substantial difference in mortality and complication rate occurred. They were supplied with information on request and this was performed once during the study.

Statistics

The administration and collection of data were based on a patient-linked trial registration number to guarantee the patients' privacy and to facilitate a blind evaluation. An Access® database was set up for collection and analysis of data. Calculations were made using SPSS 11.0® (SPSS Inc., Chicago, IL).

Principal comparisons were made on an intend-to-treat basis. In the main comparison, the pulmonary function parameters of all LCs were compared with those of all SICs. Three subgroup analyses followed. In the first, successful LCs were compared with successful SICs, in order to evaluate differences in per protocol treatments. In the second subgroup, all successful cholecystectomies were compared with all converted cholecystectomies, regardless of randomization, to demonstrate a difference between per protocol and converted procedures. Finally, the third subgroup compared converted LCs with converted SICs, in order to demonstrate any superiority of LC, even when converted. The second subgroup was also used to validate the sensitivity of the pulmonary function test.

Results of normally distributed, continuous data are presented as means with their standard deviations (SDs) in parentheses, or as medians with ranges in the case of a non-Gaussian distribution. The normality of the data was checked using the Kolmogorov-Smirnov test. Levene's test was used to check the equality of variances. When the condition of normality and equal variances was met, the t-test was used for independent

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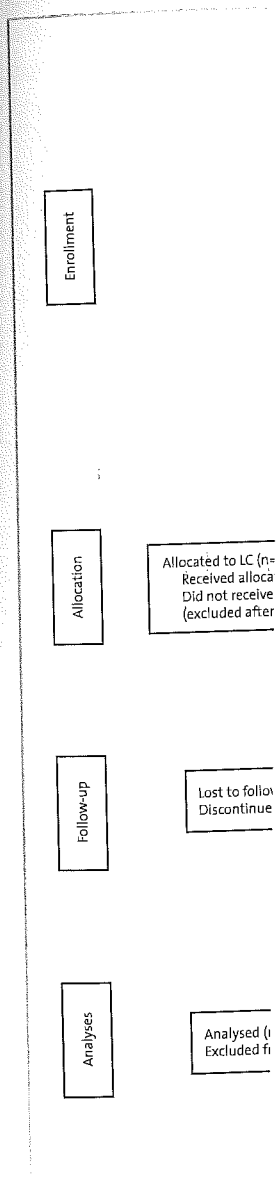

Figure 1: Revised consort state

data. When the equality of variances or normality was absent, the non-parametric Mann-Whitney U-test was used for independent data. The repeated measures analysis of variance (ANOVA) test was used to analyse the pulmonary function test results, as well as the arterial blood gas analyses, as these measurements were performed repeatedly in time. For dichotomous outcomes, the chi-squared test was used.

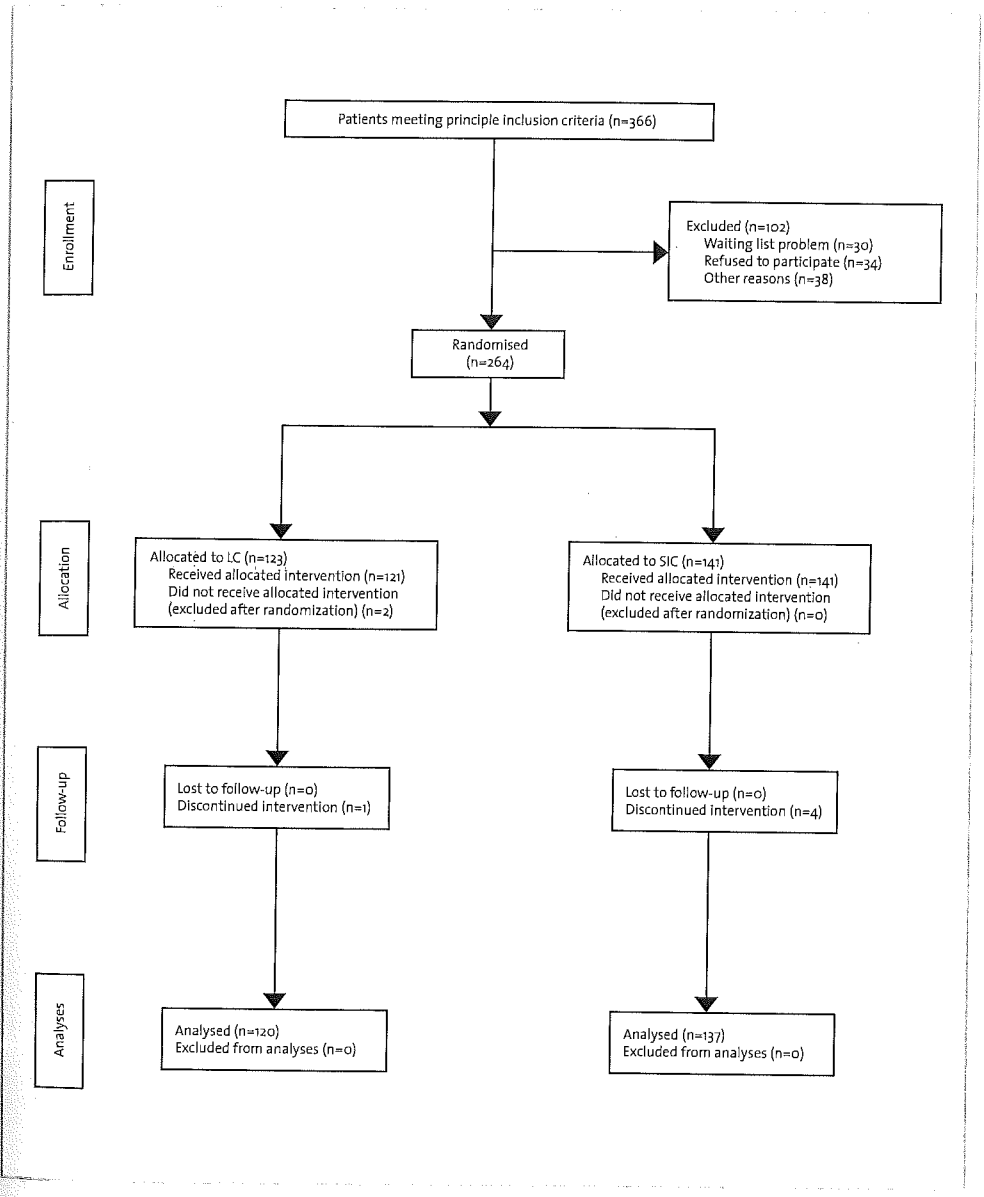

Figure 1: Revised consort statement diagram showing the flow of participants through each stage of our randomised trial [34].

RESULTS

All trial patients were included and operated on between January 2001 and March 2004. During this period, 366 patients visiting our outpatient clinic for symptomatic cholecystolithiasis fulfilled the inclusion criteria, gave informed consent, and were initially included in the trial. One hundred and two patients did not reach randomization for a variety of reasons (Figure 1). Of the remaining 264 patients, seven patients were excluded after randomization: unwilling to continue in the trial (n = 2), intra-operative suspicion of malignancy (n = 2), transfer to a nonsurgical ward (n = 1), inadvertent participation in multiple trials (n = 1), and inadequate Dutch language skills (n = 1). Two hundred and fifty-seven patients were left for analysis (LC, n = 120; SIC, n = 137; Figure 1).
The groups were similar with regard to age, sex, body mass index (BMI) and ASA classification (Table 1).

A number of anaesthesiological complications occurred in the direct peri-operative period. In the LC group, one patient became asystolic during insufflation of the pneumoperitoneum and one patient had a limited cerebrovascular accident (thrombotic) in recovery. In the SIC group, one patient developed positive cardiac enzymes compatible with ischaemia. During the post-operative period, three patients in the LC group developed phlebitis and one developed pneumonia. Although no mortalities occurred during the study, 21 (18%) and 16 (12%) complications occurred in the LC and SIC groups, respectively. The majority (16 and 13, respectively) occurred post-operatively on an incidental

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Statistical analysis
Male Female	31 (26%) 89 (74%)	30 (22%) 107 (78%)	ns
Age mean (SD) median (range)	48.4 (14.1) 49 (18-77)	48.5 (14.0) 48 (18-80)	ns
Body mass index mean (SD) median (range)	27.5 (4.8) 26.8 (27.4)	27.9 (4.6) 27.2 (25.2)	ns
ASA classification I II	81 (68%) 39 (32%)	91 (66%) 46 (34%)	ns

Table 1: Patient characteristics.

ASA, American Society of Anaesthesiologists; ns, not significant; SD, standard deviation.

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Parameter
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FEV_1 (%)
FVC (%)
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Table 2: Overview of pulmonc (SIC) patients. Results ar

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basis. Actual skin-to-skin time varied from 72 min (SD, 26 min) to 60 min (SD, 18 min) ($P < 0.001$) for LC and SIC, respectively, with total anaesthesia also being shorter for the SIC group. Conversion rates were 12% and 16%, respectively. The hospital stay was not significantly different (LC, 2.4 days (SD, 4.6 days); SIC, 3.1 days (SD, 12.4 days); $P = 0.560$). The consumption of analgesics and muscle relaxants was equal and unremarkable.

The mean pulmonary function test results for the three consecutive measurements are listed in Table 2. In both groups, an overall 20% post-operative reduction in pulmonary

Parameter		Laparoscopic Cholecystectomy (n=103)	Small-Incision Cholecystectomy (n=118)	Statistical analysis
VC_{max} (%)	*preop*	105,0 (14,0)	105,9 (15,0)	
	postop	82,7 (18,1)	81,0 (19,4)	
	follow-up	105,5 (14,5)	106,3 (15,4)	ns
FEV_1 (%)	*preop*	103,2 (15,0)	103,7 (16,2)	
	postop	80,9 (19,1)	79,8 (19,9)	
	follow-up	102,2 (15,4)	103,4 (16,6)	ns
FVC (%)	*preop*	106,2 (14,6)	107,0 (15,5)	
	postop	83,6 (19,8)	81,8 (20,6)	
	follow-up	106,0 (15,0)	107,5 (15,9)	ns
FEF_{25} (%)	*preop*	101,1 (21,6)	100,4 (24,9)	
	postop	77,6 (23,2)	77,5 (22,4)	
	follow-up	101 (22,6)	98,1 (24,5)	ns
FEF_{50} (%)	*preop*	86,4 (25,8)	86,6 (27,1)	
	postop	67,7 (23,4)	67,3 (23,5)	
	follow-up	84,8 (25,8)	84,4 (26,9)	ns
FEF_{75} (%)	*preop*	75,1 (30,1)	77,5 (30,0)	
	postop	55,6 (25,4)	57,8 (24,0)	
	follow-up	70,0 (29,5)	73,3 (30,2)	ns
PEF (%)	*preop*	103,1 (16,9)	105,2 (18,5)	
	postop	76,1 (21,4)	76,0 (20,8)	
	follow-up	104,1 (18,4)	104,8 (19,3)	ns
FIV_1 (L)	*preop*	3,50 (0,91)	3,52 (0,97)	
	postop	2,57 (0,85)	2,45 (0,73)	
	follow-up	3.59 (0,88)	3.55 (0,95)	ns

Table 2: Overview of pulmonary function results comparing laparoscopic cholecystectomy (LC) and small-incision cholecystectomy (SIC) patients. Results are presented as means (with standard deviation) of percentages of individual predictive values.

VC_{max}: maximal vital capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25}, FEF_{50}, FEF_{75}: maximum expiratory flow when 25%, 50% and 75% of the FVC has been exhaled; PEF: peak expiratory flow; FIV_1: forced inspiratory volume in 1 second; ns: not significant.

function was documented, as well as complete return to baseline at the 6-week follow-up. Statistical analysis (ANOVA) of these data showed no significant differences between the two groups for any of the eight parameters. The results are shown as a percentage of the predicted test result for the individual patient (FIV_1 in litres).

Blood gas data are presented in Table 3. Although there are statistically significant differences between the two techniques for the parameters pO_2, pCO_2, and pH, these had no influence on discharge from recovery. pO_2 was slightly lower in both groups, both in recovery (11.4 vs. 12.0 kPa for the LC and SIC groups, respectively) and on the first post-operative day (11.5 vs. 10.8 kPa, respectively), despite supplemental oxygen during the first hour of recovery in all patients. This pO_2 decrease was, interestingly, largest in the LC group. pCO_2 was higher in the recovery measurement for both groups, with a slightly larger increase in the SIC group (5.9 vs. 6.1 kPa), and a concomitant change in pH. No significant difference was found between the two groups in the time of stay in recovery (LC, 85 min (SD, 19 min); SIC, 85 min (SD, 17 min)).

Parameter		Laparoscopic Cholecystectomy (n=93)	Small-Incision Cholecystectomy (n=126)	Statistical analysis
pO_2 (kPa)	*preop*	12,5 (2,9)	12,8 (3,6)	
	recovery	11,4 (2,1)	12,0 (3,6)	p=0,025
	postop	11,5 (2,4)	10,8 (2,2)	
pCO_2 (kPa)	*preop*	5,3 (0,5)	5,3 (0,5)	
	recovery	5,9 (0,7)	6,1 (0,6)	p=0,042
	postop	5,2 (0,5)	5,2 (0,5)	
O_2 Saturation (%)	*preop*	96,9 (4,4)	97,2 (1,9)	
	recovery	96,1 (1,8)	95,8 (2,8)	ns
	postop	96,8 (2,2)	96,4 (3,6)	
pH	*preop*	7,41 (0,02)	7,41 (0,02)	
	recovery	7,34 (0,04)	7,33 (0,03)	p=0,032
	postop	7,41 (0,02)	7,41 (0,02)	
Bicarbonate (mmol/L)	*preop*	24,9 (1,9)	24,9 (2,0)	
	recovery	23,0 (2,0)	23,3 (2,0)	ns
	postop	24,1 (2,1)	24,4 (2,0)	
Base excess (mmol/L)	*preop*	0,7 (1,7)	0,8 (1,8)	
	recovery	-2,4 (1,9)	-2,3 (1,8)	ns
	postop	-0,1 (1,7)	0,3 (1,8)	

Table 3: Overview of blood gas analyses results comparing laparoscopic cholecystectomy (LC) and small-incision cholecystectomy (SIC) patients. Results are presented as means (with standard deviations) of percentages of individual predictive values.

ns: not significant; pO_2: partial oxygen pressure; pCO_2: partial carbon dioxide pressure; O_2saturation: oxygen saturation; pH: acidity.

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FEF_{50} (%)	pr
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Table 4: Overviev
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VC_{max}: maximal vital capa
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cision tectomy	Statistical analysis
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	p=0,042
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02) 03) 02)	p=0,032
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y (LC) and small-incision cholecystec-
ntages of individual predictive values.

n dioxide pressure;

Subgroup analysis comparison of the two groups, with exclusion of data from all converted cases from both groups, showed a comparable decrease in pulmonary function without clinical or significant differences.

The second subgroup analysis compared all successful procedures with all converted procedures. Analysis showed that there were significant differences in six of the eight parameters (Table 4). Conversion of either technique resulted in an average decrease in pulmonary function parameters of about 30%. Although not significantly different, the parameters FEF75 and FIV1 showed the same tendency.

Parameter		Not converted (n=189)	Converted (n=32)	Statistical analysis
VC_{max} (%)	*preop*	105,8 (14,7)	103,7 (13,5)	
	postop	83,0 (18,9)	74,1 (19,8)	p=0,012
	follow-up	106,0 (15,0)	105,2 (14,4)	
FEV_1 (%)	*preop*	103,6 (15,6)	102,6 (15,6)	
	postop	81,6 (19,1)	72,7 (20,5)	p=0,016
	follow-up	102,9 (16,4)	102,6 (13,7)	
FVC (%)	*preop*	106,9 (15,2)	105,2 (14,4)	
	postop	84,0 (20,0)	74,4 (19,8)	p=0,007
	follow-up	106,9 (15,8)	106,4 (13,9)	
FEF_{25} (%)	*preop*	100,9 (23,7)	99,4 (21,4)	
	postop	79,1 (23,0)	68,2 (18,6)	p=0,046
	follow-up	100,0 (24,3)	96,3 (19,0)	
FEF_{50} (%)	*preop*	86,5 (26,6)	86,7 (26,4)	
	postop	69,1 (23,6)	57,7 (19,8)	p=0,018
	follow-up	85 (27,0)	81,9 (22,5)	
FEF_{75} (%)	*preop*	76,8 (30,3)	73,8 (28,2)	
	postop	58,3 (24,3)	47,6 (25,0)	ns
	follow-up	72,6 (29,5)	66,8 (32,1)	
PEF (%)	*preop*	104,3 (18,0)	103,7 (16,5)	
	postop	77,3 (21,0)	68,1 (19,8)	p=0,045
	follow-up	104,7 (19,3)	103,2 (16,0)	
FIV_1 (L)	*preop*	3,54 (0,96)	3,34 (0,81)	
	postop	2,55 (0,81)	2,20 (0,59)	ns
	follow-up	3,59 (0,94)	3,44 (0,80)	

Table 4: Overview of pulmonary function results comparing converted and non-converted patients. Results are presented as means (with standard deviation) of percentages of individual predictive values.

VC_{max}: maximal vital capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25}, FEF_{50}, FEF_{75}: maximum expiratory flow when 25%, 50% and 75% of the FVC has been exhaled; PEF: peak expiratory flow; FIV_1: forced inspiratory volume in 1 second; ns: not significant.

In the third subgroup analysis, involving 14 and 22 patients from the LC and SIC groups, respectively, no significant differences between any of the eight pulmonary function parameters were found, with a slightly larger decrease in the SIC group.

The amounts of analgesics used per patient (VAS >4) during the post-operative period up to discharge, as well as the number of violations in the analgesic protocol, are reported in Table 5a, 5b. The number of potential violations was calculated based on the number of VAS measurements for each patient during the total post-operative period. Pain was regulated carefully in our hospital via the use of a nurse-driven acute pain service. Whilst in recovery, the SIC group consumed significantly more morphine per patient than the LC group, but the consumption was similar in the two groups once on the ward.

	Laparoscopic Cholecystectomy		Small-Incision Cholecystectomy		Statistical analysis
Analgesic consumption					
Visual Analogue Score available for analysis	105/120 (87%)		126/137 (92%)		
	sum (mg)	Mean consumption per patient (mg)	sum (mg)	Mean consumption per patient (mg)	
pethidine	3716	35	4634	37	ns
diclofenac	8200	78	10700	85	ns
morphine	433	4	1010	8	p<0,001

Table 5a: Overview of analgesic use in the recovery room.

	Laparoscopic Cholecystectomy	Small-Incision Cholecystectomy
Violations		
Number of violation opportunities:	856	1097
	times committed:	times committed:
No pain medication with VAS>4	35 (4,1%)	76 (6,9%)
Pain medication with VAS<4	9 (1,1%)	5 (0,5%)

Table 5b: Overview of violations of the protocol.

ns: not significant; VAS: visual analogue scale score.

DISCUSSION

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Small-Incision Cholecystectomy

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times committed:

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5 (0,5%)

DISCUSSION

The acceptance of LC as the technique of choice appears to have little foundation. Our study was set up to specifically evaluate the arguments used for this preference. It included pulmonary function changes after open upper abdominal surgery, and the suggestion that optimal pain management at the same time would further decrease pulmonary function.

Using a prospective, randomized methodology, 257 patients were analysed in an LC vs. SIC trial to determine the impact of these techniques on selected pulmonary function tests and arterial blood gas measurements.

Our findings of a comparable clinical outcome for LC and SIC are in line with other data [29]. We also found pulmonary dysfunction in the immediate postoperative period and an increased consumption of morphine in the SIC group during the post-operative period. However, this increased consumption seemed to have no clinical consequences and produced no measurable differences in pulmonary function tests or arterial blood gas analyses, although other studies have reported different results [14-20].

In some earlier clinical studies comparing LC and SIC, the methodology as well as the choice of the parameters evaluated may have skewed the results [29-32]. In order to avoid subtle opportunities for bias, strict standardization of anaesthesia management, analgesic use, and peri-operative care must be guaranteed by the protocol. Single-centre trials have a natural advantage in the standardization of treatment. Our study has addressed a number of these limitations, whilst focusing on anaesthesia and pulmonary function. Pulmonary aspects are deemed to be an important clinical reason why many anaesthesiologists prefer a laparoscopic technique over an open technique [14-16,18-20].

In the trials reported to date, only two or three pulmonary function parameters were selected. Arguments supporting this selection were absent [14-16,18-20]. Moreover, three trials suggested the superiority of a specific procedure on the basis of a difference in only one [15,19] or two [14] pulmonary function parameters. Three trials incorporated sample sizes of less than 15 patients per arm [14,18,19], and only one trial used a blind approach [18]. Details on peri-operative anaesthesia management were not provided in five trials [14-16,18,19]. One larger trial, with 64 patients in each group, found that the laparoscopic technique was superior, and included pulmonary function testing and analgesic use. However, this multicentre trial did not attempt to blind patients or physicians, details on anaesthesia management were not provided, and an incision of 10 cm was considered as small, ignoring the more acceptable 8-cm limitation [16]. Harju et al. [20] evaluated pulmonary function in only a proportion of their included patients, and found no difference between LC and SIC.

Impairment in pulmonary function was found post-operatively with no differences between the two groups. This impairment increased markedly from 20% to 30% in the converted operations for both groups, indicating that measurements by flow-volume curves are a valid tool to detect differences in pulmonary function. Considering the diversity in the literature, it is not clear whether a single pulmonary function test parameter can be designated as the most appropriate for identifying pulmonary dysfunction following upper abdominal surgery. A reduction in FEF has been suggested by some authors to be effort-independent, unlike VC, PEF, and FIV_1. Our results do not support this suggestion, as the actual changes between pre-and post-operative measurements were similar for the parameters VC_{max}, FEV_1, PEF, and the FEF series [33]. The suggestion that muscular damage and resultant pain should be designated as the factors limiting pulmonary function could also not be substantiated [11-13,28]. We noted with interest that a lower pO_2 was found in the LC group despite the lower opioid intake in this group. Although more pain medication was given to the SIC group, this was only in the immediate post-operative period and had no apparent clinical significance (Table 5A). This difference in consumption did not impact on the eligibility for discharge from recovery or hospital. Although daycare surgery is now general practice, at the time of the trial in our hospital it was not, and all patients stayed overnight. Although not an endpoint, and in recognition that this type of surgery is increasingly being performed as day-care surgery, based on the lack of a difference in recovery stay, we propose that, using the Aldrete score, and with the general requirement that patients be adequately responsive before leaving recovery, opioid consumption should not limit early discharge. For discharge eligibility in day surgery in our hospital, patients must have consumed fluids and a light meal, as well as be pain free, adequately responsive, and self-supporting. No patient is allowed to leave the hospital unaccompanied.

With the increased interest in day-care techniques, the relevance of rapid and safe surgical procedures is on the rise. A significantly shorter operative time was found in SIC. Theoretically, with increasing experience, this operative time could be reduced further, impacting on the duration of anaesthesia and allowing ample time for discharge without an overnight stay.

The one case of pneumonia should be considered a coincidence. Our findings suggest that there are no clinically relevant differences in pulmonary function following LC and SIC. As pulmonary function was measured on the first day and 6 weeks post-operatively, differences between the two techniques might have been missed during the first 2 weeks post-operatively. Future research should focus on this recovery period.

Our findings should be generally applicable in general surgical practice. The SIC procedure was associated with a shorter total anaesthesia time, no increase in complication rates,

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CONCLUSION

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and no increase in the length of hospital stay. However, ASA III and IV patients were not included in the study. In these specific populations, the clinically unimportant pulmonary function changes observed may have a much larger impact. The CO_2 burden in LC, requiring greater ventilation, in combination with decreased cardiac output, may also be relevant in ASA III and IV patients. Moreover, the anaesthetic management of SIC seems to be straightforward, and involves a decrease in some peri-operative risks attributed to the pneumoperitoneum.

Our acute pain service quickly recognized that, with good immediate post-operative pain management, the consumption of medication was low, raising the question of the need for PCA techniques for this procedure. In our study, we were unable to differentiate between the mechanisms suggested to limit pulmonary function (i.e. splinting or diaphragmatic dysfunction). Further research is needed in ASA III and IV patients to quantify pulmonary function changes.

CONCLUSION

Our study concurs with historical data, demonstrating a temporary decrease in pulmonary function in all forms of upper abdominal surgery, laparoscopic or open. This study demonstrates that SIC is comparable with LC in terms of the decrease in pulmonary function and blood gas analysis. Although initial analgesic consumption was higher in the SIC group, this did not impact on the time to discharge from recovery or the utilization of analgesia on the ward. Our study suggests that, from an anaesthesiological approach to peri-operative management, pulmonary and analgesic arguments indicate that these techniques are interchangeable when performed in an ASA I and II population.

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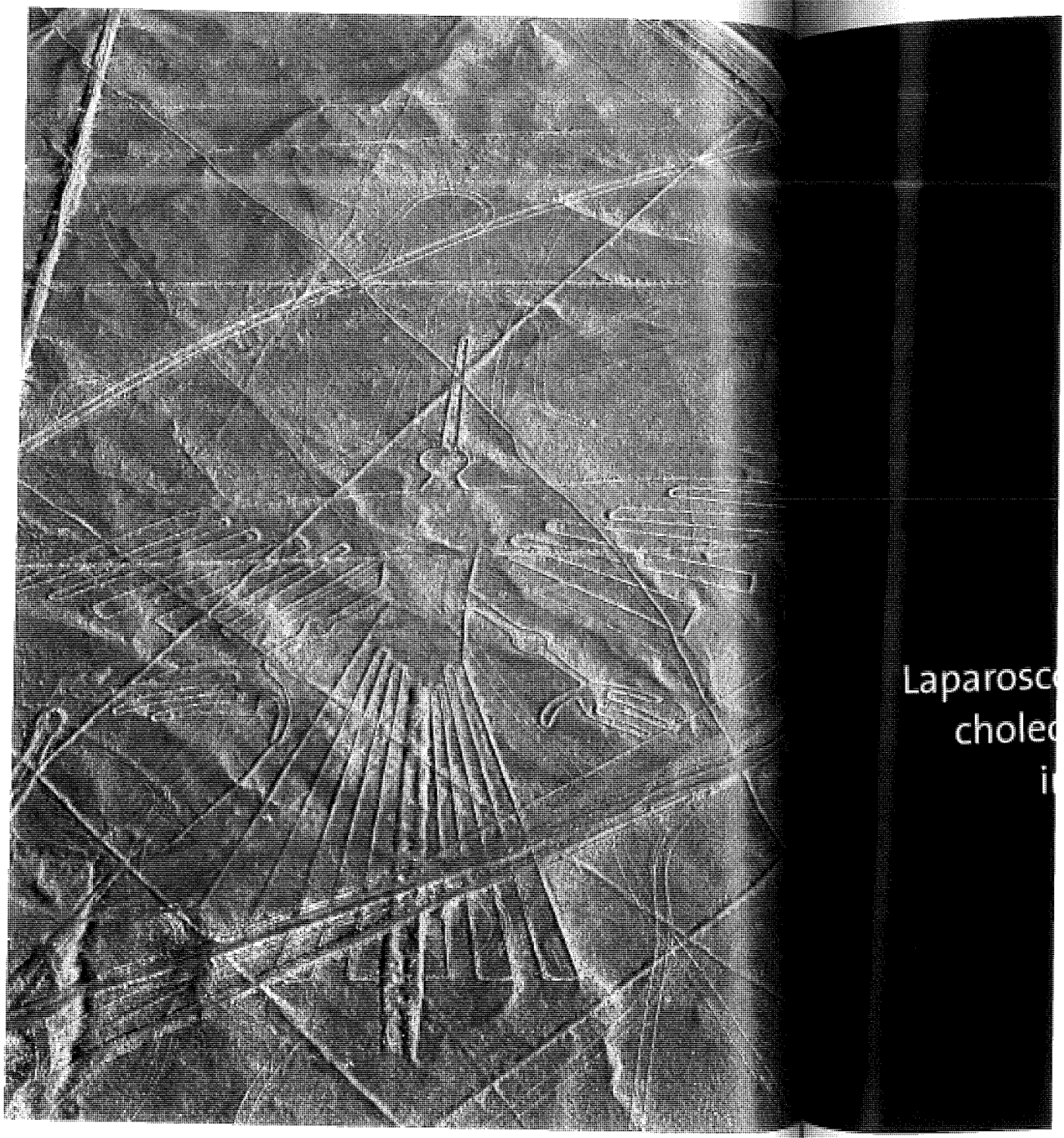

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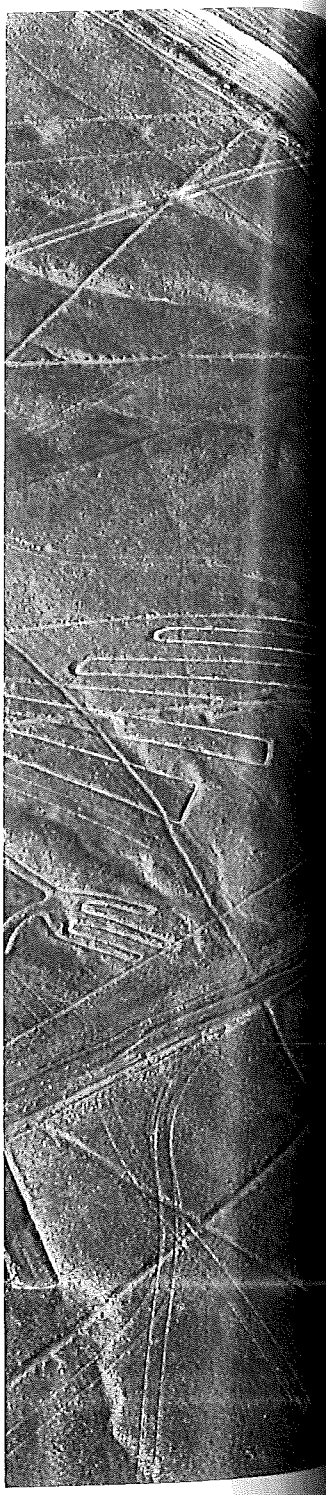

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Laparoscopic versus small-incision cholecystectomy: Health status in a blind randomised trial

F. Keus, J. de Vries, H. G. Gooszen, C. J. H. M. van Laarhoven

Surg Endosc 2008;22:1649-1659

ABSTRACT

Background

Gallstones are a major cause of morbidity, and cholecystectomy is a commonly performed procedure. Minimal invasive procedures, laparoscopic cholecystectomy (LC) and small-incision cholecystectomy (SIC), have replaced the classical open cholecystectomy. No differences have been found in primary outcome measures between LC and SIC, therefore secondary outcome measures have to be considered to determine preferences. The aim of our study was to examine health status applying evidence-based guidelines in LC and SIC in a randomised trial.

Methods

Patients with symptomatic cholecystolithiasis were included in a blind randomised trial. Operative procedures, anaesthesia, analgesics, and postoperative care were standardised in order to limit bias. Questionnaires were filled in preoperatively, the first day postoperatively, and at outpatients follow-up at 2, 6, and 12 weeks. In accordance with evidence-based guidelines, the generic short form (SF-36) and the disease-specific gastrointestinal quality of life index (GIQLI) questionnaires were used in addition to the body image questionnaire (BIQ).

Results

A total of 257 patients were randomised between LC (120) and SIC (137). Analyses were performed according to intention-to-treat (converted procedures included) and also distinguishing converted from minimal invasive (nonconverted) procedures. Questionnaires were obtained with a response rate varying from 87.5% preoperatively to 77.4% three months postoperatively. Except for two time-specific measurements in one SF-36 subscale, there were no differences between LC and SIC. There were significant differences in several subscales in all three questionnaires comparing minimal invasive versus converted procedures.

Conclusions

Applying adequate methodological quality and evidence-based guidelines (by using SF-36 and GIQLI), there are no significant differences in health status between LC and SIC.

BACKGROUND

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BACKGROUND

Cholecystectomy is a commonly performed procedure in patients with symptomatic cholecystolithiasis. With an estimated incidence up to 2.17 per thousand inhabitants [1, 2], and 500,000 cholecystectomies performed annually in the USA [3] and 21,000 in The Netherlands (an incidence of 1.31 per thousand inhabitants) [4, 5], gallstones are a major cause of morbidity in the Western world. During the 1980s, the preferred surgical technique for cholecystectomy changed from the classical open procedure to a smaller incision approach [6, 7] and eventually to laparoscopic cholecystectomy. Although evidence of superiority was never delivered, the laparoscopic technique was accepted as the gold-standard procedure by consensus [3].

Multiple randomised trials comparing laparoscopic (LC) and small-incision cholecystectomy (SIC) have been performed and results are inconsistent. Some favour the SIC technique, others favour the LC technique, and many take a neutral position. All these randomised trials are included in our Cochrane review. Our review showed no differences in primary outcome measures between LC and SIC [8].

In comparing (surgical) treatments, primary outcome measures (mortality and severe complications) have to be considered prior to secondary outcome measures. As no significant differences between LC and SIC in primary outcome measures were found [8], it is justified to consider health status, an important secondary outcome measure. Frequently, quality of life is confused with health status. Quality of life measures the subjective judgment of patients about their condition, while health status refers to the impact of disease on patients' lives in the physical, psychological, and social domains.

Questionnaires, both generic and condition-specific, have been shown to be useful in measuring changes in health status after cholecystectomy [9-11]. Several studies showed that health status was improved, both after LC and open cholecystectomy in patients suffering socially disabling uncomplicated symptomatic cholecystolithiasis [12-14]. Differences between the open and laparoscopic technique are not clear [15], although some studies found superior results using the laparoscopic technique [16, 17].

To date, differences in health status between LC and SIC are not very well examined [18-20]. Moreover, as the previous studies did not use the appropriate questionnaires as advised by evidence-based guidelines, there had been no possibility to correctly find differences in health status between both operating techniques.

The gastrointestinal quality of life index (GIQLI) and the short form (SF-36) are frequently used and validated questionnaires (disease-specific and generic, respectively) and are

most suitable for evaluating patients' functional recovery after cholecystectomy [21].

Objective

The aim of our study was to examine differences in health status in patients with symptomatic cholecystolithiasis before and after LC and SIC in a blinded randomised clinical trial. We used the GIQLI and the SF-36 questionnaires, as recommended by evidence-based guidelines [21].

METHODS

All patients with symptomatic cholecystolithiasis visiting the outpatients clinic of the St. Elisabeth hospital in Tilburg were considered for inclusion in a blind randomised trial comparing laparoscopic and small-incision cholecystectomy. Verbal and written informed consent was obtained from each patient, and patients were consecutively listed for elective cholecystectomy. Health status was a secondary outcome measure as part of the randomised clinical trial.

Sample size

No differences in primary outcome measures (mortality and complications) were expected between LC and SIC [8]. Consequently, a secondary outcome measure should be used to decide on preferences between both techniques. We decided to focus on costs between both techniques as the most important secondary outcome measure. Based on an anticipated difference of 10% in direct costs 120 patients had to be included in each group. However, multiple outcome measures including health status were evaluated in this randomised trial.

Based on a previous study [18], it was calculated that 128 patients were needed in each group to detect a difference of 5 points (assuming a standard deviation of 20) in the gastrointestinal quality-of-life index (GIQLI) questionnaire with a type I error of 0.05 and a power of 0.8.

Randomisation

As randomised trials with high bias risk may overestimate intervention effects [22], results of randomised trials with low bias risk are considered more reliable. Therefore, attention is warranted for correct generation of the allocation sequence, allocation concealment, blinding, and follow-up.

A random-number table was used for the generation of the allocation sequence and allocation concealment was guaranteed by using sealed envelopes. To eliminate bias

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caused by preoperative expectations, patients were randomised in the operation theatre after induction of anaesthesia. A telephone call to the secretary office was made and an employee opened an envelope. All patient data were recorded in a case record form, with the procedure reported as 'trial cholecystectomy'. Wounds and port sites were dressed with identical opaque dressings, stained using iodine, regardless of the surgical procedure performed, to allow blinding for patient, nurses, and physicians during the postoperative period. The type of operation was revealed just before discharge.

No patients were lost to follow-up. Operative procedures were standardised apart from using a laparoscopic or small-incision technique. Anaesthesia, postoperative care, and analgesic use were also standardised.

Inclusion and exclusion criteria

Inclusion criteria were: male or female patients with symptomatic cholecystolithiasis, age 18 years or older at recruitment, with reasonable to good health according to American Society of Anaesthesiologists (ASA) classification (ASA I or II) [23], no known relevant allergies, and a signed letter of informed consent.

Exclusion criteria were: age younger than 18 years, choledocholithiasis (icterus, acholic faeces, and/or bilirubine twice normal range), cholangitis, known pregnancy, moderate to severe systemic disease (ASA III and higher), known cirrhosis of the liver, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), psychiatric disease, or another reason (e.g. lack of knowledge of the Dutch language) for making follow-up or completion of questionnaires unreliable.

Obesity was indexed but not considered an exclusion criterion [24]. Recovery after successful endoscopic treatment of choledocholithiasis was not a contraindication. Acute cholecystitis is a different disease with other complication rates, morbidity, and conversion rates, and patients suffering acute cholecystitis were, therefore, not included.

Surgical procedures

The policy in our hospital was not to perform operative cholangiography in any patient in elective cholecystectomy. All patients had nasogastric intubations during the operation that were removed immediately afterwards. Bladder drainage was not performed. Abdominal wall and skin closure were standardised. In case of technical difficulties or for safety reasons, both laparoscopic and small-incision cholecystectomies were converted to open cholecystectomy by a subcostal incision (>8 cm). Reasons for conversion were registered. The wounds were covered with standard wound dressings as described by Majeed [24] to blind patient and ward personnel postoperatively. We did not use any local anaesthetic technique into the wounds nor intercostal nerve blocks.

Laparoscopic cholecystectomy

Open introduction of trocars was performed in all patients, regardless of previous abdominal surgery. Pneumoperitoneum was created using the subumbilical trocar with an intra-abdominal pressure up to 12 mmHg. Three trocars for instruments were inserted. The dissection of the cystic artery and cystic duct, identifying Calot's triangle, was performed using a three-point 'flag' technique [25]. The cystic duct and artery were clipped and transsected. After complete dissection of the gallbladder, it was removed either through the subumbilical or the subxyphoidal trocar. Fascia defects as a result of the insertion of 10mm trocar and the open introduction of the subumbilical trocar were closed with UR6 vicryl 1.0/2.0® sutures. All instruments, except for the subumbilical trocar, were reusable. No suction drains were left in the subhepatic space at the end of the procedure.

Small-incision cholecystectomy

In the literature most authors used 8 cm (or less) as a cut-off point to differentiate between small-incision and open cholecystectomy [24, 26-32]. Therefore, we performed small-incision cholecystectomy principally through an incision of 6 cm, maximally extended to 8 cm. As part of a separate research question, all patients had a preoperative ultrasound scan and the location of the fundus of the gallbladder was marked on the skin. We used the craniocaudal position of the mark for incision. The mediolateral position of the mark was not used, because in the pilot phase we found that the incision would be too lateral for adequate view of the hilus. The incision was placed over the musculus rectus abdominis. Only standard instruments were used and no special equipment. Access to the peritoneum was obtained by a muscle splitting (and not transsection) technique of the musculus rectus abdominis (like in an open appendectomy). The gallbladder was dissected by a fundus-first technique. If necessary the gallbladder was punctured to remove its liquid contents. The cystic duct and artery were ligated and the gallbladder was removed. No suction drains were left in the subhepatic space at the end of the procedure. Posterior and anterior fascias were closed separately with PDS 3.0® running suture. After wound closure, the length of the incision was measured. When the length exceeded 8 cm, the operation was considered to be a conversion to open cholecystectomy.

Postoperative protocol

Early oral intake and mobilization were encouraged. Patients left the hospital as soon as they felt capable. As patients were admitted at the day of operation, hospital stay was defined as the number of nights (postoperative) in hospital. Shortly before discharge, wound dressings were removed for wound inspection. For logistic reasons, we were not able to blind the surgeon at the patients' follow-up. Follow-up took place according to a standardised scheme after 2 weeks, 6 weeks, and 3 months. Patients were encouraged

to resume work and norm

Measurements

In accordance with evider
form (SF-36) and the disea
tionnaires. These questio
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The GIQLI is a disease-s
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mixed questionnaire th
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The body image quest
scales: body image, cos
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satisfaction of patient
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Internal validity (mea
to be high for both th

Statistical analysis

Analyses were perfor
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was performed: conve
procedures (LC and SI

to resume work and normal daily activity as soon as they felt capable to do so.

Measurements

In accordance with evidence-based guidelines [21], we decided to use the generic short form (SF-36) and the disease-specific gastrointestinal quality-of-life index (GIQLI) questionnaires. These questionnaires were completed preoperatively, on the first day postoperative, and at each follow-up visit after 2 and 6 weeks and after 3 months. In addition, the body image questionnaire (BIQ) was completed preoperatively and at 6 weeks postoperatively in order to estimate differences in the patients' perception of their body image and cosmetics [33].

The SF-36 is a generic health status questionnaire that has 36 questions to assess eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) [34]. Internal consistency measured by Cronbach's alpha was shown to be high (above 0.80 in all subscales) [34]. The Dutch version has been validated [35].

The GIQLI is a disease-specific health status measure. It includes both specific questions on gastrointestinal symptoms, for both the upper and the lower gastrointestinal tract, as well as questions on physical, emotional, and social capabilities [36]. It is a mixed questionnaire that includes both generic and specific questions. Based on face validity, five subscales are distinguished in addition to a total score. Internal consistency measured by Cronbach's alpha was shown to be high (above 0.90 in all subscales) [36]. The Dutch version has been validated [37].

The body image questionnaire (BIQ) consists of nine questions evaluating three subscales: body image, cosmetic, and self-confidence. The BIQ has shown to consist of two factors, a body image and a cosmetic factor [33]. The body image scale measures patients' perception of and satisfaction with their own body and explores patients' attitudes toward their bodily appearance. The cosmetic scale assesses the degree of satisfaction of patients with respect to the physical appearance of the scar. Additionally, a question is added to assess patients' self-confidence before and after surgery. Internal validity (measured by Crohnbach's alpha) reliability coefficients were shown to be high for both the body image (0.80) and cosmetic scales (0.83) [33].

Statistical analysis

Analyses were performed according to the type of operative procedure used, based on the intention-to-treat principle. Apart from this main analysis, one subgroup analysis was performed: converted procedures (LC and SIC) were compared with minimal invasive procedures (LC and SIC). This subgroup analysis was performed in order to illustrate the

sensitivity of the questionnaires. Calculations were made using SPSS version 11.0®.

Repeated measures analysis of variance (ANOVA) was used to evaluate health status differences over time between the two operative techniques.

Additional independent t-tests were performed to test for time-specific differences in scores at the preoperative measurements between two groups in order to check for a correct randomisation procedure. If appropriate, additional independent t-tests were performed to test for other time-specific differences in measurements.

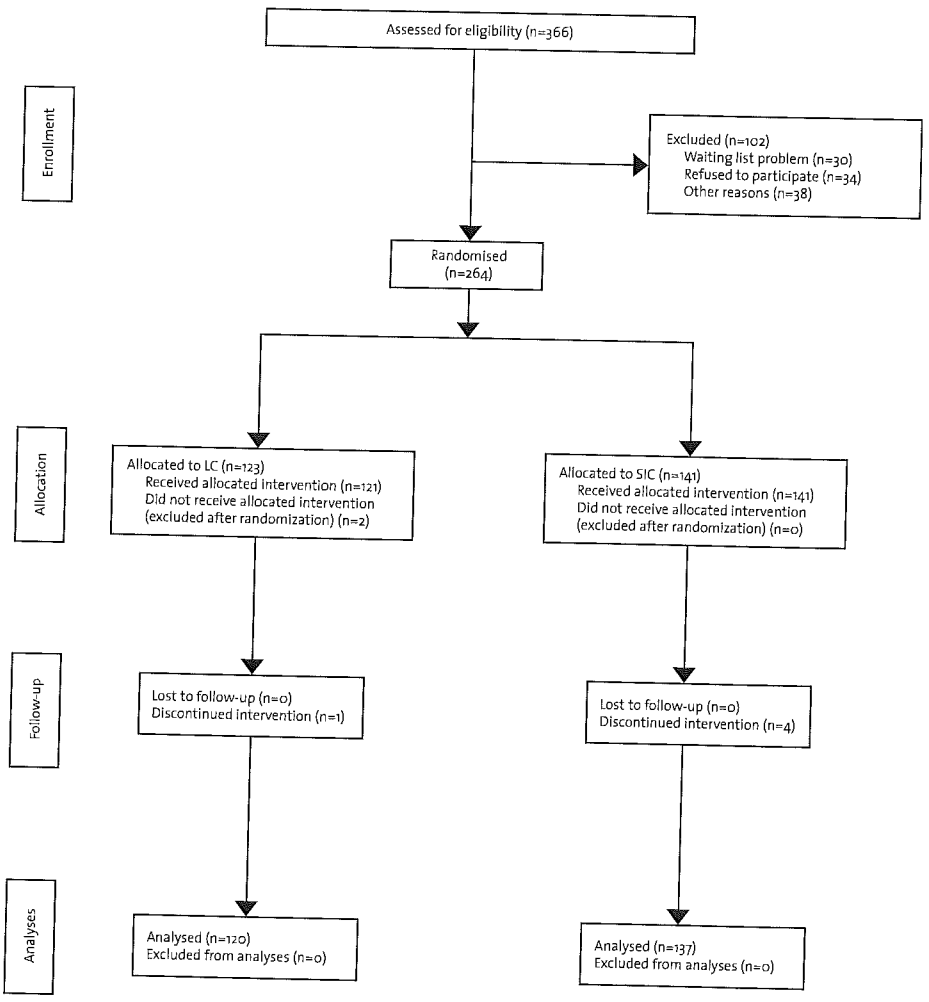

Figure 1: Revised consort statement diagram showing the flow of participants through each stage of the randomised trial [38].

RESULTS

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Male
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Age
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tage of the randomised trial [38].

RESULTS

All trial patients were included and operated between January 2001 and March 2004. Leaving unwilling and excluded patients out of consideration, 366 patients initially fulfilled the inclusion criteria and were initially included in the trial. A total of 102 patients were not randomised for a variety of reasons (Figure 1). After randomizing 264 patients, another seven patients were excluded (after their cholecystectomy) for the following reasons: unwillingness for further participation in the trial (2), intraoperative suspicion of malignancy (2), transfer to another ward not participating in the trial (1), participation in two trials (not in line with the Helsinki declaration) (1), and insufficient knowledge of the Dutch language (1). Excluding the data of these seven patients from our analyses did not affect the results of our questionnaires in any way. A total of 257 patients were left for analysis (LC:120 and SIC:137).

Baseline characteristics and operative results

The groups (LC and SIC) did not differ regarding age, sex, body mass index (BMI) and ASA classification (Table 1). The classical diagnostic symptoms of cholecystolithiasis as well as the duration of these symptoms were also equally distributed in both groups. In addition, the number of patients presenting with complicated gallstone disease who had received treatment by endoscopic retrograde cholangiopancreaticography (ERCP) (and papillotomy) were equally distributed and operated on in a later stage (Table 2).

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	P value
Male Female	31 (25.8%) 89 (74.2%)	30 (21.9%) 107 (78.1%)	0.46
Age mean (SD) median (range)	48.4 (14.1) 49 (17-77)	48.5 (14.0) 48 (18-80)	0.97
BMI mean (SD) median (range)	27.5 (4.8) 26.8 (18.5-45.9)	27.9 (4.6) 27.2 (18.0-43.3)	0.50
ASA classification I II	81 (67.5%) 39 (32.5%)	91 (66.4%) 46 (33.6%)	0.85

Table 1: Patient characteristics.

BMI: body mass index; ASA: American Society of Anaesthesiologists.

There was no mortality. There were five intraoperative complications in the LC group compared with three in the SIC group. There were 16 postoperative complications in the LC group and 13 in the SIC group. There were 21 and 16 total complications (intra- and postoperative) in the LC and SIC group, respectively. Of these, 11 and 7 complications were serious in the LC and the SIC group, respectively (Table 3). We did not find a difference in the number or severity of the complications.

Operative time was shorter for SIC compared to LC (60 versus 72 min, respectively; $U = 6013.0$, $p < 0.001$). Conversion rates were similar ($p = 0.312$), with similar reasons for

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Statistical analysis
Patients with complicated gallstone diseases before cholecystectomy	18	18	0.67
Endoscopic retrograde cholangiopancreaticography	12	13	0.89
Duration of symptoms (weeks): mean (SD) median (range)	n=107 (89.2%) 61.1 (108.8) 26 (2 - 884)	n=130 (94.9%) 70.3 (147.2) 17.5 (1 - 1040)	0.44
Incision length (mm)#: mean (SD) median (range)	N=95 (12 conversions) 76.1 (33.8) 65 (40-200)	N=134 (20 conversions) 76.0 (24.0) 66 (49-165)	0.20
Inflammation	21	25	0.88
Operative team: surgeon-resident resident-surgeon resident-resident	15 (12.5%) 84 (70.0%) 21 (17.5%)	19 (13.9%) 100 (73.0%) 18 (13.1%)	0.52 0.60 0.33
Hospital stay *: mean (SD) median (range)	2.4 (4.6) 1 (1 - 36)	3.1 (12.4) 2 (1 - 144)	0.56
Hospital stay * (without 1 extreme value): mean (SD)	2.1 (3.38)	2.04 (2.42)	0.88
Employed (n)	50	51	
Return to work (weeks): mean (SD) median (range)	4.1 (2.3) 4 (1-12)	3.7 (2.0) 3 (0.5-12)	0.30

Table 2: Operative features and difficulties of laparoscopic and small-incision cholecystectomy.

*#conversions were included in incision length measurements; *hospital stay in postoperative nights.*

conversion. The follow-
Follow-up was 91.4-96.3
six weeks or three mont

There were no differenc
the GIQLI subscales, the

Health status

The questionnaires were

Laparoscopic Cholecystecto
Intraoperative complication
Asystole
Common bile duct (CBD) in hepatico-jejunostomy, com prolonged ICU stay, stenosi
Bleeding requiring conversi
Bowel injury at introductio
Cerebrovascular accident a
Total intraoperative
Postoperative complicatio
Pneumonia
Cerebrovascular accident (é
Intra-abdominal fluid coll (haematoma); icterus (ER complicated by bleeding)
Pancreatitis (conservative
Intra-abdominal abscess
Epididimitis (operation b
Total postoperative

Table 3: Serious complica

CBD: common bile

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omplications (intra- and
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). We did not find a diffe-

;us 72 min, respectively;
, with similar reasons for

ncision /stectomy	Statistical analysis
	0.67
	0.89
,94.9%) .7.2) 1040)	0.44
(20 conversions) 4.0) -165)	0.20
	0.88
)%)).0%) %)	0.52 0.60 0.33
4) 14)	0.56
1.42)	0.88
) 12)	0.30

ion cholecystectomy.

in postoperative nights.

conversion. The follow-up rate between the groups was not statistically different. Follow-up was 91.4-96.3% at six weeks, 82.2-82.8% at three months and 100% at either six weeks or three months. Complaints at follow-up were comparable.

There were no differences in the preoperative measurements of the SF-36 subscales, all the GIQLI subscales, the total GIQLI score, and the BIQ subscales.

Health status

The questionnaires were obtained with a response rate varying from 87.5% preoperatively

Laparoscopic Cholecystectomy	11	Small-Incision Cholecystectomy	7
Intraoperative complications		**Intraoperative complications**	
Asystole	1	Cardiac ischemia, no elevated enzymes	1
Common bile duct (CBD) injury, eventually hepatico-jejunostomy, complicated prolonged ICU stay, stenosis bile duct.	1	CBD injury, conversion, T-drain, ERCP and papillotomy for CBD stone	1
Bleeding requiring conversion (and transfusion)	1	Hepatic parenchyma rupture, conservative treatment (transfusion)	1
Bowel injury at introduction (sutured)	1		
Cerebrovascular accident at recovery	1		
Total intraoperative	5	**Total intraoperative**	3
Postoperative complications		**Postoperative complications**	
Pneumonia	1	Cystic duct leakage (ERCP + stent)	1
Cerebrovascular accident (6 weeks postoperative)	1	CBD injury, multiple relaparotomies and ICU stay	1
Intra-abdominal fluid collection (haematoma); icterus (ERCP: no stones, complicated by bleeding)	1	CBD stone (ERCP) and abscess intra-abdominal (ultrasound drainage)	1
Pancreatitis (conservative treatment)	1	CBD stone with pancreatitis (ERCP)	1
Intra-abdominal abscess (re-laparoscopy)	1		
Epididimitis (operation by urologist)	1		
Total postoperative	6	**Total postoperative**	4

Table 3: Serious complications in laparoscopic and small-incision cholecystectomy (intraoperative and postoperative).

CBD: common bile duct; ICU: intensive care unit; ERCP: endoscopic retrograde cholangiopancreatography.

to 77.4% three months postoperatively. The nonresponders did not differ from those who remained in the study with regard to complications (16%), operative time (65 minutes), hospital stay (1.5 days), return to work (3.2 weeks) or baseline scores.

When comparing LC with SIC (intention-to-treat), we found no differences in all SF-36

		Preoperative	Postoperative day 1	2 weeks	6 weeks	12 weeks	P value
SF-36							
physical	LC	77.0 (23.0)	57.1 (29.5)	67.5 (23.2)	83.2 (21.2)	87.8 (17.4)	0.413
	SIC	83.0 (18.3)	39.9 (29.8)	63.0 (22.8)	83.1 (20.8)	87.5 (19.3)	
social	LC	43.4 (14.2)	77.8 (19.9)	70.7 (23.9)	86.5 (19.3)	91.9 (15.9)	0.260
	SIC	42.7 (17.1)	74.3 (22.6)	66.3 (25.8)	82.3 (22.9)	90.4 (19.0)	
role physical	LC	56.4 (43.4)	52.6 (43.2)	26.7 (36.4)	67.4 (40.1)	81.1 (34.9)	0.667
	SIC	60.8 (44.4)	53.0 (45.7)	29.5 (49.4)	54.8 (42.6)	79.2 (35.8)	
role emotion	LC	73.7 (39.4)	70.5 (38.8)	68.3 (41.7)	82.7 (33.6)	88.6 (27.8)	0.797
	SIC	74.3 (39.7)	70.3 (40.7)	66.4 (54.9)	80.7 (36.5)	88.7 (29.4)	
mental	LC	61.7 (11.8)	75.0 (17.1)	77.3 (18.3)	83.3 (16.2)	85.1 (16.6)	0.558
	SIC	62.0 (10.9)	72.1 (18.9)	74.5 (18.7)	81.2 (18.4)	83.4 (17.4)	
vitality	LC	54.1 (11.0)	59.6 (22.4)	52.1 (21.1)	67.8 (20.1)	73.5 (20.4)	0.767
	SIC	53.8 (12.2)	58.4 (22.9)	51.8 (21.6)	66.9 (22.6)	72.7 (21.7)	
pain	LC	56.5 (19.5)	55.6 (22.5)	52.2 (21.7)	74.7 (20.2)	82.4 (21.5)	0.429
	SIC	54.6 (17.1)	55.9 (24.6)	46.4 (21.9)	69.3 (23.8)	83.1 (21.4)	
general health	LC	56.1 (11.7)	69.7 (17.3)	71.8 (19.3)	74.9 (22.0)	76.3 (21.2)	0.457
	SIC	57.4 (11.3)	65.1 (19.2)	70.1 (20.1)	72.5 (21.5)	76.4 (19.2)	
health change	LC	57.7 (21.2)	57.7 (21.2)	62.0 (26.9)	76.7 (23.9)	77.1 (24.4)	<0.001*
	SIC	55.4 (20.4)	55.4 (20.4)	53.5 (27.5)	64.6 (25.1)	71.5 (27.2)	
GIQLI							
physical	LC	2.79 (0.76)	2.82 (0.73)	2.78 (0.75)	3.20 (0.62)	3.31 (0.59)	0.790
	SIC	2.95 (0.74)	2.67 (0.83)	2.69 (0.75)	3.14 (0.73)	3.30 (0.63)	
gastrointestinal	LC	3.01 (0.59)	3.01 (0.54)	3.22 (0.48)	3.46 (0.41)	3.50 (0.42)	0.247
	SIC	3.12 (0.58)	3.13 (0.55)	3.22 (0.45)	3.46 (0.46)	3.52 (0.40)	
social	LC	2.89 (0.48)	2.82 (0.42)	2.81 (0.52)	2.93 (0.37)	2.97 (0.29)	0.056
	SIC	2.90 (0.42)	2.82 (0.43)	2.76 (0.56)	2.85 (0.50)	2.85 (0.38)	
mental	LC	2.55 (0.55)	2.59 (0.45)	2.88 (0.41)	3.04 (0.35)	3.07 (0.37)	0.561
	SIC	2.65 (0.49)	2.58 (0.55)	2.74 (0.45)	2.99 (0.47)	3.04 (0.44)	
total	LC	102.4 (17.0)	102.6 (14.8)	108.5 (15.0)	116.4 (11.9)	118.3 (11.7)	0.607
	SIC	106.7 (14.9)	104.5 (16.0)	107.4 (14.0)	116.7 (13.2)	118.0 (11.1)	
BIQ							
body image	LC	6.42 (1.98)	-	-	6.03 (1.90)	-	0.530
	SIC	6.26 (1.89)	-	-	5.85 (1.35)	-	
cosmetic	LC	-	-	-	18.38 (3.88)	-	0.100
	SIC	-	-	-	17.52 (3.55)	-	
self-confidence	LC	6.95 (1.27)	-	-	7.68 (1.21)	-	0.647
	SIC	7.02 (1.28)	-	-	7.49 (1.15)	-	

Table 4: Comparison of GIQLI, SF-36, and BIQ scores in laparoscopic (LC) and small-incision cholecystectomy (SIC) according to intention-to-treat (mean scores and SD).

** significant difference.*

subscales, except for 'p
favouring the laparosco
time-specific analyses,
weeks ($p < 0.001$) posto
regard to the four GIQLI

SF-36	
physical	min-inv
	conv
social	min-inv
	conv
role physical	min-inv
	conv
role emotion	min-inv
	conv
mental	min-inv
	conv
vitality	min-inv
	conv
pain	min-inv
	conv
general health	min-inv
	conv
health change	min-inv
	conv
GIQLI	
physical	min-inv
	conv
gastrointestinal	min-in
	conv
social	min-in
	conv
mental	min-in
	conv
total	min-in
	conv
BIQ	
body image	min-in
	conv
cosmetic	min-in
	conv
self-confidence	min-i
	conv

Table 5: Comparison of GIQLI, pn

** significant difference;*

not differ from those
;), operative time (65
seline scores.

lifferences in all SF-36

	P value
12 weeks	
87.8 (17.4)	0.413
87.5 (19.3)	
91.9 (15.9)	0.260
90.4 (19.0)	
81.1 (34.9)	0.667
79.2 (35.8)	
88.6 (27.8)	0.797
88.7 (29.4)	
85.1 (16.6)	0.558
83.4 (17.4)	
73.5 (20.4)	0.767
72.7 (21.7)	
82.4 (21.5)	0.429
83.1 (21.4)	
76.3 (21.2)	0.457
76.4 (19.2)	
77.1 (24.4)	<0.001*
71.5 (27.2)	
3.31 (0.59)	0.790
3.30 (0.63)	
3.50 (0.42)	0.247
3.52 (0.40)	
2.97 (0.29)	0.056
2.85 (0.38)	
3.07 (0.37)	0.561
3.04 (0.44)	
118.3 (11.7)	0.607
118.0 (11.1)	
-	0.530
-	
-	0.100
-	
-	0.647
-	

lecystectomy (SIC) according

subscales, except for 'perceived health change'. There were significant differences favouring the laparoscopic technique ($F = 16.054$, $df = 1$; $p < 0.001$) (Table 4). Performing time-specific analyses, differences were identified at two weeks ($p = 0.029$) and six weeks ($p < 0.001$) postoperatively. There were no differences between LC and SIC with regard to the four GIQLI subscales, the total GIQLI score, and the body image subscales.

		Preoperative	Postoperative day 1	2 weeks	6 weeks	12 weeks	P value
SF-36							
physical	min-inv	79.9 (21.3)	50.1 (30.9)	67.3 (22.1)	83.5 (21.1)	87.6 (18.9)	0.046*
	conv	82.3 (17.5)	31.6 (24.9)	45.5 (22.6)	79.6 (19.3)	87.8 (14.6)	
social	min-inv	43.2 (15.5)	76.7 (21.3)	69.9 (24.1)	85.1 (20.9)	90.9 (18.1)	0.214
	conv	41.7 (18.3)	70.1 (21.9)	55.1 (29.0)	76.1 (24.7)	93.2 (13.8)	
role physical	min-inv	60.2 (43.4)	54.0 (44.5)	27.9 (36.3)	61.3 (41.7)	79.9 (35.2)	0.415
	conv	46.9 (46.8)	43.1 (43.9)	31.0 (87.6)	55.0 (44.1)	81.8 (37.1)	
role emotion	min-inv	74.9 (39.0)	72.1 (38.8)	67.4 (41.5)	82.1 (34.6)	89.3 (28.1)	0.373
	conv	66.7 (42.8)	56.5 (45.4)	66.7 (93.7)	76.7 (40.6)	83.3 (32.1)	
mental	min-inv	61.8 (11.6)	73.8 (17.9)	76.6 (17.5)	82.7 (16.4)	84.9 (15.9)	0.413
	conv	62.6 (9.1)	70.8 (19.5)	69.0 (25.5)	77.1 (24.4)	78.6 (23.8)	
vitality	min-inv	54.0 (11.9)	59.5 (22.8)	53.1 (21.1)	67.8 (21.4)	73.3 (20.6)	0.180
	conv	53.2 (8.8)	55.0 (21.2)	41.6 (21.1)	63.3 (21.6)	71.1 (24.9)	
pain	min-inv	55.6 (18.4)	56.5 (23.7)	50.4 (22.1)	72.5 (22.3)	82.9 (21.7)	0.038*
	conv	55.2 (17.7)	49.6 (22.2)	37.1 (17.4)	65.4 (22.4)	81.9 (18.5)	
general health	min-inv	56.8 (11.4)	68.2 (18.1)	72.0 (19.4)	74.2 (21.3)	76.9 (19.7)	0.136
	conv	56.3 (12.4)	59.7 (19.6)	61.0 (20.2)	67.8 (25.1)	72.2 (23.3)	
health change	min-inv	56.8 (20.8)	56.8 (20.8)	58.8 (27.5)	71.7 (24.9)	74.9 (26.3)	0.066
	conv	54.2 (20.4)	54.2 (20.4)	46.3 (24.7)	56.3 (24.2)	67.1 (23.6)	
GIQLI							
physical	min-inv	2.90 (0.72)	2.78 (0.76)	2.79 (0.71)	3.19 (0.65)	3.33 (0.60)	0.007*
	conv	2.67 (0.96)	2.40 (0.96)	2.20 (0.87)	2.96 (0.91)	3.10 (0.71)	
gastrointestinal	min-inv	3.09 (0.57)	3.10 (0.54)	3.23 (0.47)	3.47 (0.43)	3.52 (0.39)	0.052
	conv	2.89 (0.68)	2.89 (0.56)	3.08 (0.37)	3.42 (0.50)	3.46 (0.50)	
social	min-inv	2.89 (0.46)	2.83 (0.42)	2.83 (0.51)	2.90 (0.43)	2.92 (0.35)	0.003*
	conv	2.90 (0.35)	2.75 (0.45)	2.35 (0.62)	2.74 (0.58)	2.85 (0.35)	
mental	min-inv	2.60 (0.53)	2.58 (0.50)	2.84 (0.41)	3.04 (0.38)	3.06 (0.38)	0.031*
	conv	2.63 (0.45)	2.64 (0.53)	2.48 (0.57)	2.81 (0.70)	2.96 (0.63)	
total	min-inv	104.9 (16.0)	104.3 (15.0)	108.9 (14.3)	117.1 (11.5)	118.4 (11.0)	0.020*
	conv	101.4 (17.0)	97.8 (17.8)	98.5 (13.3)	111.2 (19.5)	115.8 (14.0)	
BIQ							
body image	min-inv	6.31 (1.80)	-	-	5.75 (1.27)	-	<0.001*
	conv	6.60 (2.78)	-	-	7.55 (3.04)	-	
cosmetic	min-inv	-	-	-	18.27 (3.54)	-	<0.001*
	conv	-	-	-	14.86 (3.97)	-	
self-confidence	min-inv	7.08 (1.16)	-	-	7.60 (1.13)	-	0.064
	conv	6.31 (1.83)	-	-	7.38 (1.60)	-	

Table 5: Comparison of GIQLI, SF-36, and BIQ scores in minimal invasive laparoscopic (LC) and small-incision cholecystectomy (SIC) procedures versus converted (LC and SIC) procedures (mean scores and SD).

** significant difference; min-inv: minimal invasive procedures (LC and SIC); conv: converted procedures (LC and SIC).*

Subgroup analysis

In checking for differences in preoperative data in the minimal invasive procedures versus conversions comparison, we only found a significant difference in the self-confidence subscale of the body image questionnaire ($t = 2.821$, $df = 207$, $p = 0.005$) with higher self-confidence scores in the minimal invasive operated group (7.08 versus 6.31). No other differences were found in preoperative data.

In order to assess differences between minimal invasive procedures (both laparoscopic and small-incision) and procedures converted to the classical open cholecystectomy, we examined patients' scores across the follow-up period (Table 5).

There were significant differences in the SF-36 subscales 'physical functioning' ($F = 4.057$, $df = 1$; $p = 0.046$) and 'pain' ($F = 4.391$, $df = 1$; $p = 0.038$). In the GIQLI questionnaire, there were significant differences in the total score ($F = 5.593$, $df = 1$; $p = 0.020$), and in the 'physical' ($p = 0.007$), 'social' ($p = 0.003$), and 'mental' ($p = 0.004$) subscales. Also, in the BIQ there were significant differences in the 'body image' and 'cosmetic' subscales between both operative groups, favouring the minimal invasive procedures ($F = 13.939$, $df = 1$; $p < 0.001$). No other differences were found.

DISCUSSION

We have used both generic and disease-specific health status questionnaires and a body image questionnaire to evaluate the effect of LC versus SIC in patients having cholecystectomy for symptomatic cholecystolithiasis. No differences were found between laparoscopic and small-incision cholecystectomies (applying intention-to-treat). However, with regard to minimal invasive or converted procedures, we found significant differences in the 'physical' subscales in both SF-36 and GIQLI as well as differences in body image in favour of minimal invasive procedures. The fact that significant differences were found in the 'physical' subscales in both questionnaires illustrates construct validity between both health status instruments.

Literature

A few other studies have compared health status after LC and SIC [18-20]. Two studies found that the laparoscopic technique was associated with a more rapid improvement in health status after cholecystectomy compared with the small-incision technique [18, 19]. One study found no differences at all between both techniques [20]. However, it is difficult to draw conclusions from three studies that used different questionnaires and suffer several methodological flaws. None of the mentioned studies combined the SF-36 and GIQLI as advised by evidence-based guidelines [21].

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Barkun studied 35 and 23 patients in the LC and SIC groups, respectively, and used the same GIQLI as we did in addition to the Nottingham health profile (NHP) and a visual analogue scale (VAS) for health [18]. Allocation concealment was unclear, no blinding was used, and eight dropouts occurred in their rather small, preliminary stopped trial. They used cumulative totals of both GIQLI and NHP data instead of using subscales. Changes in one dimension might be offset by changes in other dimensions. Both questionnaires have more than one dimension (the cumulative total); subscales indeed provide the advantage of additional information on several dimensions. As a rather small number of patients were included (the trial was stopped preliminary), no subscales were assessed, and no considerations were given to the construct or divergent validity of both questionnaires, their conclusion that LC was associated with a significantly quicker return to 'good health' seems inappropriate based on their results.

McMahon compared health status in 151 and 148 laparoscopic and small-incision cholecystectomy patients respectively using the SF-36 health survey questionnaire and the hospital anxiety and depression scale (HADS) [19]. Generation of the allocation sequence in their trial was unclear and no blinding was used. They found that patients recovering from LC enjoyed significantly better health 1 and 4 weeks after the operation compared with those recovering from SIC, but no significant difference was found at 12 weeks. The absence of preoperatively baseline measurements and the absence of considerations on the construct or divergent validity of the questionnaires make conclusions about postoperative data uncertain. Differences in SF-36 and HADS correlated with differences in return to domestic and leisure activities, but were not translated in differences in paid activity.

Squirrell used the NHP in 100 patients (50 in each group) preoperatively, and 3 weeks and 6 months postoperatively [20]. This was the only study that used blinding in their methods. Generation of the allocation sequence in their trial was unclear. At no time there was a significant difference between the two groups. The study used a rather small sample size, and unfortunately they did not use a disease-specific questionnaire, but only one generic questionnaire. They concluded that it is necessary to take a broader view of health and not concentrate simply on pain when assessing postoperative recovery.

In our study, no significant differences were found between LC and SIC using both generic and disease-specific health status as well as body image with response in approximately 80% of patients. The response rate of 77.4% at 3 months follow-up may represent a possible source of bias. However, the nonresponders were comparable to those who remained in the study with regard to complications, operative time, hospital stay, return to work, and baseline scores of questionnaires. Moreover, our response rate is in line with the response rates in the studies of Barkun et al. (58%) and McMahon et al. (78%).

We conclude that there are no differences between both operative techniques regarding health status. The only exception is that in the SF-36 subscale perceived health change we found a difference between LC and SIC, which appeared to be caused by the scores at 2 and 6 weeks postoperatively and disappeared at 3 months follow-up. LC patients reported a larger health change. However, in the evaluation of 17 aspects of health status, only one difference was found. Moreover, this difference in perceived health change was not reflected in an earlier return to work in LC. In contrast, SIC patients returned to work quicker than LC patients, although this different was not significant. Therefore, our overall interpretation is that there are no differences between LC and SIC.

The comparable 'physical' subscales in SF-36 and GIQLI, which are supposed to measure the same effect, are both significantly different in the minimal invasive versus conversions comparison illustrating construct validity of both questionnaires. Subscales on different subjects in the questionnaires illustrate divergent validity. Significant differences between minimal invasive and converted procedures illustrate that the questionnaires used are able to measure what they are intended to do.

CONCLUSION

In our randomised trial with adequate generation of the allocation sequence, concealment of allocation, blinding, and follow-up we used both a generic and a disease-specific questionnaire in addition to a body image questionnaire. There is no significant difference in health status measured with SF-36, GIQLI, and BIQ between laparoscopic and small-incision cholecystectomy (applying the intention-to-treat principle). Additional calculations showed a significant difference between minimal invasive LC or SIC procedures and procedures converted to the classical open cholecystectomy.

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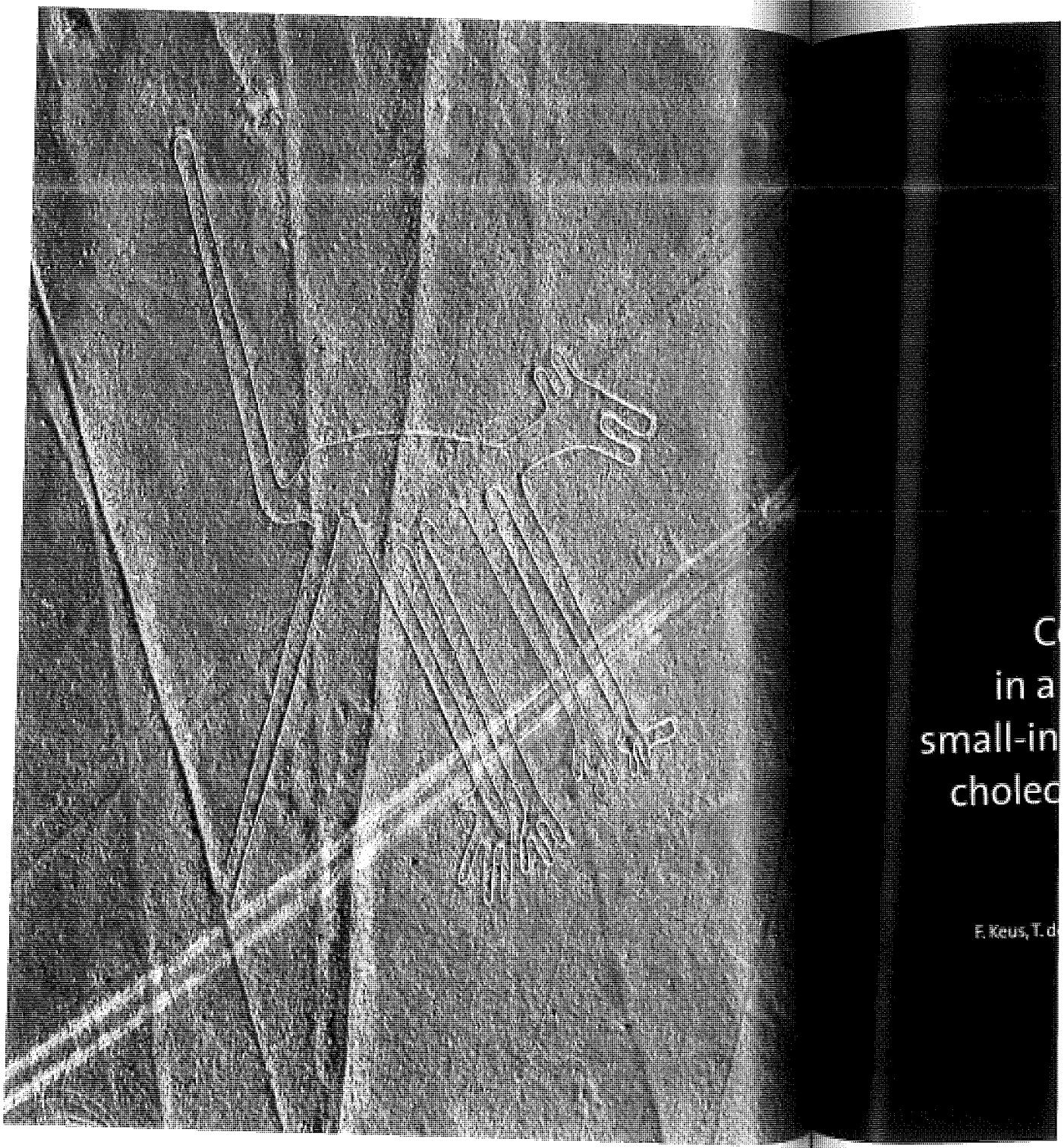
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Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal

F. Keus, T. de Jonge, H. G. Gooszen, E. Buskens, C. J. H. M. van Laarhoven

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ABSTRACT

Background

After its introduction, laparoscopic cholecystectomy rapidly expanded around the world and was accepted the procedure of choice by consensus. However, analysis of evidence shows no difference regarding primary outcome measures between laparoscopic and small-incision cholecystectomy. In absence of clear clinical benefit it may be interesting to focus on the resource use associated with the available techniques, a secondary outcome measure. This study focuses on a difference in costs between laparoscopic and small-incision cholecystectomy from a societal perspective with emphasis on internal validity and generalisability

Methods

A blinded randomized single-centre trial was conducted in a general teaching hospital in The Netherlands. Patients with reasonable to good health diagnosed with symptomatic cholecystolithiasis scheduled for cholecystectomy were included. Patients were randomized between laparoscopic and small-incision cholecystectomy. Total costs were analyzed from a societal perspective.

Results

Operative costs were higher in the laparoscopic group using reusable laparoscopic instruments (difference 203 euro; 95% confidence interval 147 to 259 euro). There were no significant differences in the other direct cost categories (outpatient clinic and admittance related costs), indirect costs, and total costs. More than 60% of costs in employed patients were caused by sick leave.

Conclusion

Based on differences in costs, small-incision cholecystectomy seems to be the preferred operative technique over the laparoscopic technique both from a hospital and societal cost perspective. Sick leave associated with convalescence after cholecystectomy in employed patients results in considerable costs to society.

Trial registration

ISRCTN Register, number ISRCTN67485658.

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BACKGROUND

Langenbuch's classical cholecystectomy has been the gold standard for over a century [1]. Since the mid 1970s surgeons began shortening their incisions because of a presumed quicker convalescence [2,3]. Soon thereafter, laparoscopic cholecystectomy (LC) was introduced, and rapidly expanded around the world [4]. The popularity of this procedure was partly based on an appealing technological innovation as well as industry driven motives and not primarily a result of an evidence-based approach [5].

Analysis of evidence in Cochrane reviews shows no difference regarding primary outcome measures (mortality and complications) between the three operative techniques of cholecystectomy (open, small-incision, and laparoscopic) [6-8]. In absence of clear clinical benefit based on these meta-analyses it may be interesting to focus on the resource use associated with the available techniques. We performed a single blind randomized clinical trial focusing on a secondary outcome: costs. In a previous paper we emphasized intrinsic validity of this trial, proved reproducibility of results from other trials, and showed generalisability in a general teaching hospital [9].

The costs of LC and small-incision cholecystectomy (SIC) have been compared in six randomized trials [10-15]. These available studies are inconsistent in outcome and conclusions, use different perspectives, and most of the trials suffer methodological shortcomings.

The research question is whether there is a difference in costs from a societal perspective between small-incision and laparoscopic cholecystectomy using a blind randomized approach. In a detailed cost analysis attention has to be paid to both direct and indirect costs as well as the perspective of the analysis. Furthermore, cost prices, budget prices, and tariffs have to be distinguished.

METHODS

In meta-analyses we found no major differences in clinical outcome measures (mortality, complications, conversions, hospital stay, and convalescence) between LC and SIC for patients with symptomatic cholecystolithiasis [8]. We also found no differences considering pulmonary function, health status, and cosmesis [16,17]. Costs are a secondary outcome measure and ultimately may be a decisional factor. This paper focuses on cost-minimization analysis.

Medical Ethics Committee approval for this single-centre trial was obtained in September

2000. Between January 2001 and January 2004, all patients referred to our surgical outpatient's clinic with symptomatic cholecystolithiasis (confirmed by ultrasonography) were considered for inclusion in this study.

Inclusion- and exclusion criteria

Inclusion criteria were male or female patients with symptomatic cholecystolithiasis, aged 18 years or older at recruitment, reasonable to good health (ASA I or II), no known relevant allergies, and a signed informed consent letter.

Exclusion criteria were age younger than 18 years, choledocholithiasis (icterus, acholic faeces, and/or bilirubine of twice normal range), cholangitis, known pregnancy, moderate to severe systemic disease (ASA III and higher), known cirrhosis of the liver, history of abdominal malignancy, previous upper abdominal surgery (precluding a laparoscopic approach), psychiatric disease, or a reasons (e.g. lack of knowledge of the Dutch language) that might make follow-up or completion of questionnaires unreliable.

Obesity was not an exclusion criterion. Recovery after successful endoscopic treatment of choledocholithiasis was not a contra-indication. Acute cholecystitis was excluded.

Randomization

A random number table was used for generation of the allocation sequence [18] and the allocation concealment was guaranteed by using sealed envelopes. Patients were randomized after induction of anesthesia. An employee of the secretary office opened an envelope. Details were recorded in a case record form. Otherwise the procedure was recorded as 'trial cholecystectomy'.

Surgical procedures

All patients had a standard anesthesia regime. Premedication, medications for induction and continuation of anesthesia, as well as respiration during surgery were standardized. Residents (from 2nd year on) performed most of the operations. In case of technical difficulties either trial technique could be converted to open cholecystectomy (OC). Wounds were covered with standard wound dressings [19]. In this way blinding of patients, nurses, and ward physicians was achieved. Postoperative analgesics and medication for nausea were standardized.

Open introduction was performed in all laparoscopic cholecystectomies. Pneumoperitoneum was created with an intra-abdominal pressure up to 12 mmHg. Three trocars for instruments were inserted. The dissection of the cystic artery and cystic duct, identifying Calot's triangle, was performed using a three points 'flag' technique [20]. The cystic duct and artery were clipped and transected. All instruments were reusable.

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In concordance with literature a cut-off point of 8 cm was used to differentiate between SIC and OC [14,19,21-26]. The incision was placed over the musculus rectus abdominis. No special equipment was used. Access to the peritoneum was obtained by a 'muscle splitting' technique. The gallbladder was dissected by a 'fundus-first' technique. The cystic duct and artery were ligated and the gallbladder was removed. Posterior and anterior fascias were closed separately. If the length of the incision exceeded 8 cm, the operation was considered to be a conversion to OC.

Postoperative protocol

Early oral intake and mobilization were encouraged. Patients left the hospital as soon as they were able to do so. Incidental 'social' reasons for lengthening of hospital stay (by a few days) were accepted. Hospital stay was defined as the number of postoperative nights in hospital. For logistic reasons, we were not able to blind the surgeon during follow-up. Follow-up was standardized after 2 weeks, 6 weeks, and 3 months. Patients were encouraged to resume work as soon as possible.

Analysis and sample size

In meta-analyses no differences in patient-relevant outcomes appear to be present between these two techniques. Assuming no differences in primary outcome measures, sample size calculation was based on anticipated differences of costs. The direct costs of the first 50 patients in the trial were calculated so as to estimate the likely range of differences in costs and their standard deviations. On this basis, we estimated that 120 patients per group would be needed to detect a difference of 10% in direct costs using an α of 0.05 and a β of 0.9.

Analyzing differences in costs due to complications between both techniques would require another sample size including thousands of patients in order to possibly find significant results. Consequently, differences in complication costs were therefore not statistically tested in our study. However, these costs were reported to illustrate their impact on total costs.

Statistics

All data were stored in a case record form (Access®) based on a patient-linked trial registration number. A double data entry was performed. Comparisons were made on an intention to treat basis. Calculations were made using SPSS 11.0®.

The chi-square test was used for dichotomous outcome. Normality of data was checked using the Kolmogorov-Smirnov test [27]. Levene's test was used for checking equality of variances. When the condition of normality and equal variances was met, the t-test for independent data was used; otherwise the nonparametric Mann-Whitney U test for

independent data was used.

Methods of cost analysis

As cost items that are equally present in both groups do not contribute to differences, it can be argued that these can be left out of consideration. On the other hand all costs contribute to the total amount and the incremental value. Therefore, we strived for reporting costs in detail [28]. For each cost item, hospital costs, overhead costs, and consultants' costs were included if appropriate (Table 1).

All costs were calculated in euros (2004). All direct medical costs were summarized in different categories including costs due to complications (admittance, operative, outpatients' clinic, and complications).

As there are no relevant or significant differences in clinical outcome [8,16] or quality-of-life [17], a cost-minimization analysis seems most appropriate. Afterwards, differences in costs can be balanced with other (thus far unknown) differences in outcome.

In evaluating costs, it is important to be complete in accounting for all items [29]. Therefore, in general a societal perspective is recommended [30-32]. In a societal perspective all costs are included in the analysis (patient, hospital, and losses in production), irrespective of the stakeholder incurring the costs or who benefits from treatment. Moreover, today's limited health care budgets warrant proper economic evaluation of treatments, especially when incidences and impact on economy are high (like in symptomatic cholecystolithiasis).

Definitions of cost categories

Direct medical costs: costs resulting from outpatient clinic, hospital admittance, surgery, complications, etcetera.

Direct non-medical costs: costs arising from outside health care immediately related to treatment (e.g. traveling costs from patients). The problem is that it is very difficult to estimate these costs accurately in all patients. We assume that these costs are equal for both groups. Moreover, since the vast majority of patients have an uncomplicated recovery, these costs are assumed not to contribute importantly to total costs.

Indirect non-medical costs: costs due to loss of productivity related to employment status of patients. These costs arise from loss of productivity caused by sick leave, disabled for work, or mortality. We decided to use the friction cost method [31-36].

Tariffs, cost prices, budget prices and overhead costs

In cost assessments tariffs, cost prices, and budget prices have to be distinguished.

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Preoperative
Operative
Admittance
Follow-up
Complications

Table

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Tariffs are costs that are calculated for insurance companies. Tariffs are nearly always different from real costs. Budget prices on the other hand are figures used for internal

Item	
Preoperative	General practioner
	First visit to outpatient clinic (20min)
	X-thorax *
	ECG
	Blood examinations
	Consultation pulmonologist (36min)
	Consultation cardiologist (22.65min)
	Consultation internist (30min)
	ERCP (30min)
	Ultrasound * (10min)
Operative	Hospital operating room per minute
	Anaesthesiologist per minute#
	Surgeon per minute
	Surgical resident per minute
	Laparoscopic instruments - reusable
	Laparoscopic instruments - disposable
Admittance	Ultrasound localization of gallbladder
	Blood gas analysis (Åstrup)
	Spirometry analysis
	One night hospital stay
	One night medium care (including intensivist)
	Intensive care (with mechanical breathing)
	Intensive care (without mechanical breathing)
	Pathology examination
Follow-up	Outpatients visit (10min)
Complications	Ultrasound drainage (10min)
	Blood culture
	Blood transfusion
	Urologist outpatients visit (30min)
	Gastroscopy (30min)
	MRCP *
	CT abdomen *
	CT thorax *
	CT angiography *
	CT cerebrum *
	MR cerebrum *
	Re-laparotomy
	Emergency department visit
	Ultrasound duplex

Table 1: List of cost items used in calculations of total costs. For each cost item hospital costs, overhead costs and consultants costs are included if appropriate.

**Time spend by radiologists at diagnostic procedures was estimated at 10 minutes; #In our hospital anaesthesiologists are responsible for two operations at a time. Therefore, 140 euro (per hour) was calculated for two operations resulting in 1.17 euro per minute per operation. Time spend by consultants (for diagnostic procedures) in brackets.*

(hospital) calculations, and do not reflect real costs either. Cost prices are real costs for procedures and are usually not used in hospital administrations. These cost prices can be calculated but are sometimes difficult to retrieve.

Apart from these differences there are costs for depreciation and interest. Different methods are used and no uniform guidelines exist how to estimate these overhead costs, neither do arguments exist that one method is superior over the other. In our hospital a percentage incremental value is added to every cost price. We applied this method in our study.

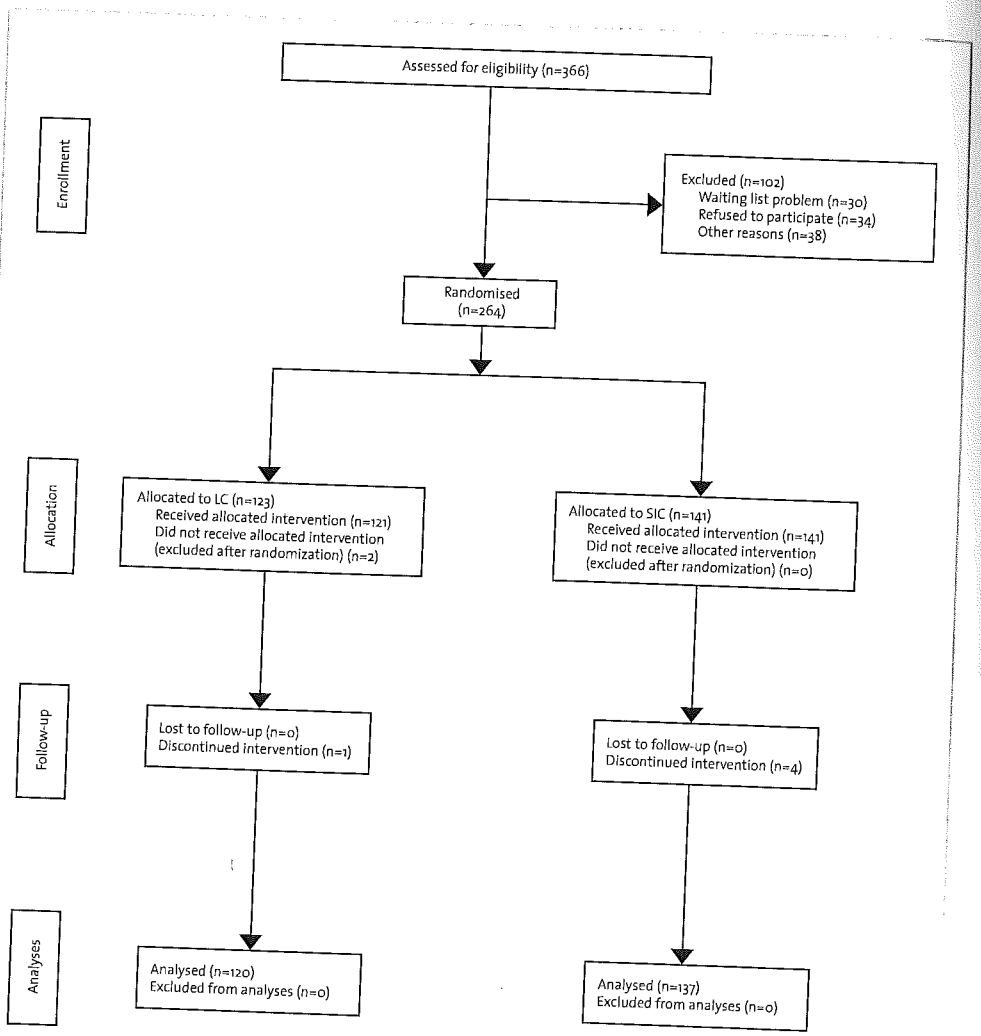

Figure 1: Revised consort statement diagram showing the flow of participants through each stage of the randomized trial [37].

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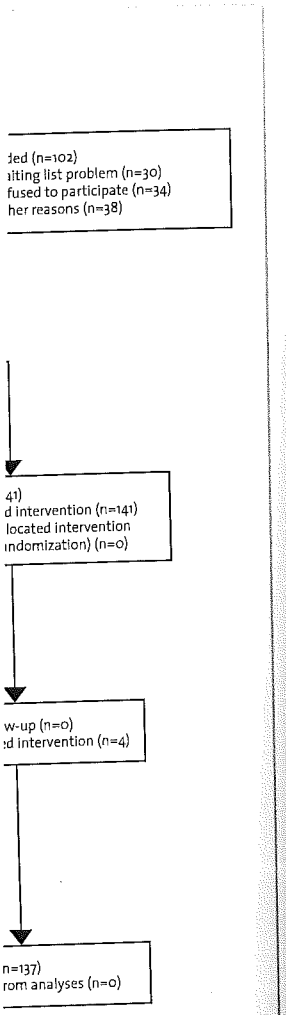

:h stage of the randomized trial [37].

Description of procedures and measurement of resources

In this cost-minimization analysis, all resources were prospectively recorded. A visit to the general practitioner, diagnostic examinations, and costs due to preoperative outpatient clinic visits were counted. Hospital stay was counted as the number of overnights stay. Medication use is included in admittance cost prices. Operative costs and the costs of anesthesiologists were calculated according to operating room occupancy. Standard materials and equipment used in the operating room including costs associated with cleaning and sterilisation are included in hospital costs for surgery. The costs of the surgeon and resident were calculated from the time of incision to last suture. In laparoscopic instruments extra laparoscopy-specific materials like clips and endobags were calculated, but monitor, gass-insufflator, and camera were not calculated as these were considered present. In the small-incision procedure no extra equipment other than standard instruments is needed. In follow-up the time of the surgeon was calculated. Finally, if complications occurred, all extra costs were included. Costs of consultants were calculated using the national agreed honorarium (140 euro per hour) (Table 1).

Sensitivity analyses

Several sensitivity analyses were performed to yield an impression of the effect of changes on total costs. Variables were considered if the costs were appreciable and a change in the costs of the variable could be possible and clinically relevant:

1. The influence of the use of disposable instead of reusable laparoscopic instruments on total costs.
2. Influence of reduction of time back-to-work by one week on total costs.
3. Influence of the reduction of hospital stay by one night on total costs.

RESULTS

All trial patients were included and operated between January 2001 and March 2004. Leaving unwilling and excluded patients out of consideration, 366 patients visiting the outpatient clinic of the hospital for symptomatic cholecystolithiasis fulfilled the inclusion criteria and were initially included in the trial. A total of 102 patients were not randomized for a variety of reasons (Figure 1) [37]. After randomizing 264 patients, another 7 patients were excluded for the following reasons: unwilling to continue in the trial (n = 2), intra-operative suspicion of malignancy (n = 2), transfer to a non-surgical ward (n = 1), inadvertent participation in multiple trials (n = 1), and inadequate Dutch language skills (n = 1). A total of 257 patients were left for analysis (LC:120 and SIC:137).

The two treatment groups did not differ regarding age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification (Table 2). None of the 257

patients were lost to follow-up and resources of all patients could be determined.

The numbers of converted procedures, hospital stay, the number of residents performing the procedure, and the number of intra-operative and postoperative complications were not significantly different. Operative time was significantly shorter in the small-incision group (difference 11 minutes, 95% confidence interval (CI) 6 to 17 minutes; $p < 0.001$) (Table 3). The total costs for both treatment groups including all 257 patients are summarized (Table 4).

There is an important difference in direct costs. The difference is caused by differences in costs due to complications and rendering total costs in favor of the laparoscopic procedure.

The difference in operation theatre cost is in favor of the SIC group however. Operation theatre costs are over 23% more expensive in the LC group compared to the SIC group (LC: 1112 euro compared to SIC: 901 euro; difference 211 euro, $p < 0.001$). Indirect costs are higher in the laparoscopic group.

Data of costs are non-Gaussian distributed, importantly influenced by one extreme outlier. Therefore, although intention-to-treat is violated, the results excluding one outlier in each group are also shown (Table 4). Results in the cost categories admittance and outpatients' clinic do not change. There still is a difference in operation theatre costs in favor of the SIC group (difference 203 euro; 95% CI 147 to 259 euros). In the total costs, there is a difference in favor of the SIC group. All patients were operated using reusable

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Statistical analysis
Male / Female	31 / 89	30 / 107	p=0.459
Age mean (SD) median (range)	48.4 (14.1) 49 (17-77)	48.5 (14.0) 48 (18-80)	p=0.974
BMI mean (SD) median (range)	27.5 (4.8) 26.8 (18.5-45.9)	27.9 (4.6) 27.2 (18.0-43.3)	p=0.500
ASA classiffication I II	82 (68.3%) 38 (31.7%)	91 (66.4%) 46 (33.6%)	p=0.855

Table 2: Patient characteristics.

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Conversion rate

Operative team
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resident-resident

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laparoscopic instruments and costs were calculated accordingly.

In order to be able to compare uncomplicated LC and SIC procedures, costs were also calculated excluding all complicated cases. There still are differences present in the operation theatre related costs (difference 199 euro; 95% CI 139 to 259 euro; $p < 0.001$) and in total direct costs (difference 139 euro; 95% CI 42 to 237 euro; $p = 0.006$). No significant differences were observed in other direct cost categories, indirect costs, and total costs.

In order to estimate the influence of indirect costs on total costs we performed calculations only including employed patients (Table 5). Indirect costs appear to amount over 60% of total costs in both groups.

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Statistical analysis
Mortality	0	0	
Complications	21	16	p=0.119
intra-operative	5	3	p=0.363
postoperative	16	13	p=0.331
Failed symptom relief	11 (9.2%)	14 (10.2%)	p=0.777
Operative time (min):			
mean (SD)	71.9 (25.8)	60.4 (18.3)	p<0.001
median (range)	68.5 (26-215)	60.0 (29-105)	
Conversion rate	14 (11.7%)	22 (16.1%)	p=0.312
Operative team			
surgeon-resident	15 (12.5%)	19 (13.9%)	p=0.515
resident-surgeon	84 (70.0%)	100 (73.0%)	p=0.596
resident-resident	21 (17.5%)	18 (13.1%)	p=0.331
Hospital stay*			
mean (SD)	2.4 (4.6)	3.1 (12.4)	p=0.560
median (range)	1 (1 - 36)	2 (1 - 144)	
Hospital stay* (without 1 extreme value)			
mean (SD)	2.1 (3.4)	2.0 (2.4)	p=0.877
Number of patients with:			
1 night stay postoperative	67 (55.8%)	62 (45.3%)	p=0.091
2 nights stay postoperative	38 (31.7%)	56 (40.9%)	p=0.127

Table 3: Comparison of clinical results.

* *hospital stay: in postoperative nights.*

We performed a sensitivity analysis assuming the use of disposable instead of reusable laparoscopic instruments. Calculations show increase of operation costs resulting in

	Laparoscopic Cholecystectomy	Small-Incision Cholecystectomy	Difference in costs (per patient)	Significance
All patients included (intention-to-treat)	(n=120)	(n=137)		
Direct costs (per patient)	305760 2548	452654 3304	-756	P=0,006*
Outpatients clinic related (per patient)	54293 452	62627 457	-5	P=0.640
Operation theatre related (per patient)	133406 1112	123404 901	211	P<0.001*
Admittance related (per patient)	67972 566	81707 596	-30	P=0.342
Complications related	50089	184917		
Indirect costs	(n=50)	(n=51)		
(per patient)	172005 3440	155024 3040	400	P=0.315
Total costs (per patient)	477765 3981	607678 4436	-454	P=0.737
Without one outlier in each group	(n=119)	(n=136)		
Direct costs (per patient)	272584 2291	282683 2079	212	P=0.006*
Outpatient clinic related (per patient)	53980 454	62273 458	-4	P=0.669
Operation theatre related (per patient)	130796 1099	121856 896	203	P<0.001*
Admittance related (per patient)	67421 567	81131 597	-30	P=0.346
Complications related	20388	17423		
Indirect costs	(n=50)	(n=51)		
(per patient)	172005 3440	155024 3040	400	P=0.315
Total costs (per patient)	444589 3736	437706 3218	518	P=0.034*

Table 4: Overview of costs with all patients included and without one extreme value in each group (in euro).

**significant difference. Negative differences in costs favour the laparoscopic procedure and positive differences in costs favour the small-incision technique.*

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differences of approximately 960 euro in favor of the SIC group (95% CI 912 to 1024 euro; $p < 0.001$).

A sensitivity analysis assuming a decrease in work leave by 1 week for the employed patients (n = 101) in this trial results in savings of 82790 euro. In another sensitivity analysis assuming a decrease in hospital stay by 1 night for the employed patients (n = 101) in this trial results in savings of 22980 euro.

DISCUSSION

When no differences in primary outcomes are found, consequently, several secondary outcome measures like operative time, hospital stay, and time to recovery as well as costs can be chosen as focus for a trial. Most of these secondary outcome measures are incorporated in a total cost assessment. Our cost analyses show that SIC is more expensive compared to LC when all patients are included (intention to treat, Table 4). Excluding one outlier from analyses in each group, total costs per patient are higher in

	Laparoscopic Cholecystectomy (n=120)	Small-Incision Cholecystectomy (n=137)	Difference in costs (per patient)	Significance
60 and older	26	26		
Employed	50	51		
Unemployed / unknown	44	60		
Employed	n=50	n=51		
Direct costs	(37.7%)	(38.4%)		
(per patient)	104003 2080	96454 1891	189	P=0.055
Indirect costs	(62.3%)	(61.6%)		
(per patient)	172005 3440	155024 3040	400	P=0.315
Average period before return to work (in weeks (SD):	4.2 (2.3)	3.7 (2.0)		P=0.298
Total costs	276008	251477		
(per patient)	5520	4931	589	P=0.179

Table 5: Overview of costs with employed patients only (in euro).

Total indirect costs: 327029 euro (n=101). Average period before return to work: 4.0 (SD: 2.2) weeks. Average indirect costs per patient per week: 820 euro. Negative differences in costs favour the laparoscopic procedure and positive differences in costs favour the small-incision technique.

the LC group (p = 0.034). This difference is caused by a difference in operative costs (difference 203 euro; 95% CI 147 to 259 euro; p < 0.001) and a difference in indirect costs (p = 0.315). When all complicated cases are excluded, direct costs (p = 0.006) and operative costs (199 euro, p < 0.001) per patient remain higher in the LC group (using reusable laparoscopic instruments).

The problem in reporting costs are non-Gaussian distributions. Following intention-to-treat principles, complicated cases should be included to obtain an objective impression of absolute costs. Using means results in a biased impression of falsely increased measures as a consequence of skewed data, while using medians would ignore complicated cases since in cholecystectomy about 80% of operations are uneventful procedures (Table 4). In our trial one extreme outlier occurred. Differences in techniques have to be distinguished from random variations. Meta-analyses demonstrate no differences in complications between laparoscopic and small-incision cholecystectomy. We therefore believe that differences in complication costs should be considered random variations. Moreover, our trial was not powered to detect differences in complication costs and these results should be considered a spurious finding and should therefore not be statistically tested at all. Reporting costs excluding one outlier in each group might therefore be more correct as it incorporates complication costs but prohibits distortion of total costs by random extreme outliers.

There are several problems in analyzing and pooling cost results from different studies. First of all, costs are reported in different ways including different cost items. A second problem is that different points of views are taken. These different perspectives make comparison of studies difficult. A third problem is the difference in validity of the cost assessments, defined by the details in which costs are calculated. More detailed analyses are known for more reliable estimates, while less detailed studies cause severe bias [28,29]. A fourth problem in comparing studies is that there may be considerable differences in local costs. Specific items in cost analyses differ from one country or even setting to another. A fifth and probably most important problem are cultural differences. There are wide variations in convalescence (and return to work) between different cultures depending on a multitude of causes, like social security and cultural habits [38,39]. As multiple factors cause heterogeneity, pooling results seems inappropriate and one may only draw general conclusions from individual studies.

In literature six trials report costs and lack of methodological quality was present in several trials [10,12,14,40]. In some trials methodology of cost assessment was very limited described [12,40]. Outpatients' costs [11,12] and indirect costs [10-12,14] are excluded in several studies making overall (societal) comparison of techniques incomplete. Retrospective analyses [14] or expert settings [11,14] raise questions on reliability

and generalisability. In our trial surgical residents performed 86% of the operations.

The trials by Calvert and Nilsson are high quality trials [11,13]. Unfortunately, outpatients' clinic costs and indirect costs are not included in the trial by Calvert [11]. Additionally, median hospital stay and estimated operative time (instead of individual data) are used for calculations. They concluded that hospital costs using the laparoscopic technique were 29% higher [11]. The trial by Nilsson is a high quality multi-centre trial. However, standardization of procedures is less biased and more uniform in a single-centre trial compared to a multi-centre trial. Costs are reported in medians (ignoring outliers and complications). This study found lower direct costs and higher indirect costs for the SIC group [13].

Some conclusions of differences in costs were based on differences in hospital stay [10] or convalescence [13,14]. However, in meta-analysis no differences were found in hospital stay and convalescence between both techniques [8]. The differences in indirect costs in our trial should be considered as random variations caused by random differences in age and sex between both groups in the employed patients: calculated friction costs per hour per employee are higher for male and for higher aged employees.

Remarkably, the trials with lack in methodological or cost assessment quality [10,14,40] favor the laparoscopic technique, while the trials with high methodological quality or more detailed cost assessments [11,13] favor the small-incision technique. This linkage between unclear/inadequate methodological quality to significant overestimation of beneficial effects and underreporting of adverse effects is in concordance with other studies [8,41,42].

Different parties have different interests in cost analyses. Though, all perspectives belong to our society. Advantages of a certain therapy in a societal perspective should be given more importance compared to other perspectives not including all cost categories. It provides the most comprehensive assessment and is most relevant for national policy decisions. Implementation at a local level, however, may require to also taking into account a hospital perspective as financial consequences will become visible.

Feasibility of ambulatory cholecystectomy [43,44] and the wide range in return to work from a few days to 12 weeks raises questions on potential savings. Possibilities for future savings by reduction of hospital stay (direct costs), irrespective of the operating technique for cholecystectomy, were compared to savings by reduction of sick leave (indirect costs). Assuming 21000 cholecystectomies in the Netherlands, reducing hospital stay by one night (50%) in every patient would result in potential savings of 4.8 million euro in the Netherlands annually. Assuming that 50% of the cholecystectomy patients

are employed (Table 5), reducing sick leave by one week (25%) in every employed patient would lead to savings of 8.6 million euro on a national basis annually. Based on these hypothetical figures it seems easier to achieve savings by earlier return to work instead of reducing hospital stay. Moreover, as more than 60% of costs of employed patients are caused by sick leave it is more logical to focus on this cost category.

Assuming 21000 cholecystectomies in the Netherlands and an employment ratio of 50%, calculations of sensitivity analyses on hypothetical savings were performed considering change in policy from disposable to reusable laparoscopic instruments, change from LC to SIC, or reducing sick leave by one week. As a result savings of approximately 16 million, 4.2 million, and 8.6 million euro respectively are possible on a national basis annually. However, conclusions have to be careful since calculations are hypothetical.

CONCLUSION

In this single-centre trial with representative results and emphasis on methodological quality LC appears more costly: the procedural costs surpass those of SIC (and use of disposable instruments would only further increase this difference). Thus SIC is the preferred operative technique over LC both from a hospital and societal cost perspective.

Sick leave associated with convalescence after surgery results in considerable costs to society especially in the employed patient.

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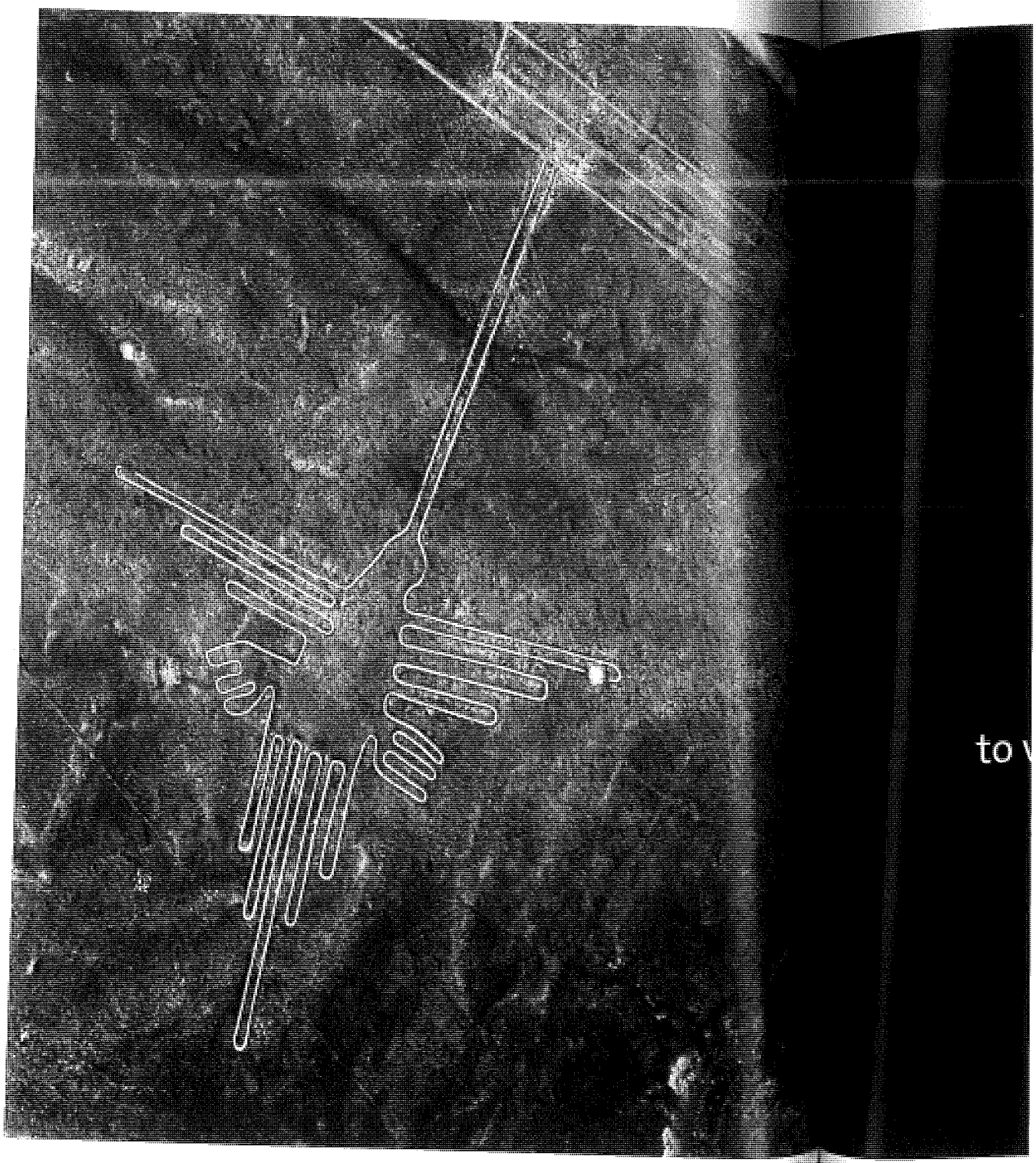

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Assessing factors influencing return back to work after cholecystectomy: a qualitative research

F. Keus, J. de Vries, H. G. Gooszen, C. J. H. M. van Laarhoven

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ABSTRACT

Background

Cholecystectomy causes considerable financial burden on society with a major part caused by sick-leave. There are wide variations in duration of sick-leave. The aim of our study was to identify all aspects that influence the moment of return to work by using focus groups and to compare responses from patients and physicians.

Methods

A qualitative research design was planned using focus group discussions. Four focus group discussions were organized: two patient groups and two physician groups. Employed patients who had recovered after cholecystectomy were included in the patient groups. The physicians groups consisted of general practitioners, surgeons, and company physicians. Three investigators independently searched transcriptions of the sessions for all items relating to return to work. The importance of items and categories were assessed by determining frequencies.

Results

In the patients groups physical limitations (35.3%) and individual patient factors (17.5%) were important factors in the duration of sick-leave, while influence or advice comprised only 8.4% of the items. In the physicians groups influence or advice (21.8%) and information-related factors (21.4%) were thought to be important categories.

Conclusions

Physicians perceive their advices as an important factor in patients' duration of sick-leave. In contrast, patients seldom mention this factor and experience physical complaints as the major reason influencing the moment of return to work.

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BACKGROUND

For about 100 years, open cholecystectomy (OC) was considered a safe standard [1]. Reduction in the length of the incision, known as small-incision cholecystectomy (SIC), with a concomitant reduction in postoperative morbidity, has been reported as early as the mid 1970's [2,3]. However, before the SIC could find general acceptance, the laparoscopic cholecystectomy (LC) was introduced in the late 1980's [4]. This procedure gained rapid and immense popularity [5] and became the surgical treatment of choice even though its superiority was not in evidence [6].

Both minimal invasive techniques (SIC and LC) are preferred over the open technique because of a quicker convalescence (hospital stay and return to work) [7,8]. As no significant differences between LC and SIC in primary outcome measures were found [9], secondary outcome measures should further decide on preferences.

The financial burden of cholecystectomy on society is considerable with over 60% of the total costs of employed patients caused by indirect costs related to sick-leave of employees [10]. As time before return to work ranges from 1 to 10 weeks, both in successful LC and successful SIC [11], apparently other unknown factors are involved. The question arising is who or what influences the moment of return to work?

To answer this question, we have to know a wide range of factors that influence the absence from work. In the literature, patients' expectations [12], low job satisfaction, physical effort at work, pain, patient's expectation of slow recovery, expectation of no financial loss [13], a longer period of work incapacity before the intervention, older age, and longer hospital stay [14], are factors already identified in extending sick leave. The impact of cultural differences on the moment of return to work was shown as well [15]. These studies examined the influence of specific factors on the moment of return to work. However, as far as we know no attempt has been made to determine a wide range of factors that are involved.

Focus group discussions appeared to be a reliable method of gathering qualitative information on a subject [16,17]. A focus group is a type of group interview with the primary goal to generate ideas about a particular issue. The reliance in focus groups is on the interaction between the various participants [16]. The dynamic interplay of participants replaces their interaction with the interviewer, leads to a greater emphasis on the participants' point of view [18], generates additional ideas in the group, and is the additional value of focus group discussions compared to individual (patient) interviews.

The aim of our study was to retrieve a wide range of aspects that influence the moment of return to work after cholecystectomy and to compare responses from patients and physicians. This was done using focus groups. We hypothesize that a physicians' advice is important in the decision to return to work.

METHODS

Participants

We organized four focus group discussions: two patient groups (seven patients each) and two physician groups (seven and eight physicians). Patients were randomly sampled from the patients included in our randomized clinical trial on outcome after laparoscopic and small-incision cholecystectomy [11]. Approval from the Medical Ethics Committee was obtained (ISRCTN67485658; http://isrctn.org). The indication for cholecystectomy in all patients was symptomatic cholecystolithiasis. The results and postoperative outcome of the patients in our trial were in line with results in literature [11]. A paid job was an inclusion criterion in patient groups. A second inclusion criterion was that patients should have had their cholecystectomy at least six months earlier to guarantee full recovery. In both patient groups, there were patients operated on by three techniques: laparoscopic, small-incision, and procedures converted to conventional cholecystectomy.

Physicians who come in contact with this type of patients and, thus, can influence in some way the moment of return to work of patients are: general practitioners, surgeons, and company physicians. Company physicians are doctors who independently advice patients and employers when work should be restarted or which alternative work may be performed by the patient when unable to restart their usual activities. All three types of physicians were present in both physician groups. Physicians were randomly sampled from a list representing the hospitals' affiliation area. They were invited to participate in the focus groups according to availability. These physicians were not physicians for these particular patients.

In total four focus groups were run, two patients groups and two physicians groups. One patients' focus group comprised of 4 men and 3 women and the other patients' focus group consisted of 1 man and 6 women. All patients had their cholecystectomy at least six months earlier. Participants in the first physicians' focus group were two company physicians, three general practitioners, and two surgeons. In the second physicians focus group there were two company physicians, four general practitioners, and two surgeons. Informed consent was obtained from all participants.

Compared with the second patients' focus group, in the first patients' focus group more

patients had remaining complaints and symptoms. However, the items mentioned in these two focus groups were the same. Therefore, the three investigators felt that saturation was reached after only two sessions. The same occurred in the physicians focus groups.

Method of group discussion

The focus groups were run by the authors and all investigators were present in all four focus group sessions. In accordance with focus group methodology, the role of the investigator leading the focus group was restricted to procedural issues (e.g. making sure that every participant had the chance for expression of his/her opinion) and posing the two opening questions in order to let the interaction between participants dominate the discussion.

The two opening questions in the patients' focus groups were: (1) how did the patient experience his/her cholecystectomy, and (2) who or what factors did influence the moment of return to work.

The two opening questions in the physicians' focus groups were: (1) how do the physicians think that patients experienced their cholecystectomy, and (2) who or what do physicians think influences the moment of return to work in patients.

The patient group discussion was started by the opening question how patients had experienced and felt about their operation. At the end of a discussion around a question, the investigator summarized the items that were mentioned and asked patients if there were items they could think of that had not yet been mentioned. Consequently, the other opening question was posed.

Data recording

During the discussions, items were noted on a flip-over by one of the investigators. In addition, the sessions were audiotaped with permission from the patients. These tapes were subsequently verbatim transcribed.

Assessing the number of focus groups

The number of focus group sessions was determined by saturation, i.e., when in another group no new items are mentioned by the participants in comparison to a previous similar focus group. When saturation is reached, the number of focus groups is considered to be adequate.

Analysis

Analysis of results in qualitative research is completely different from classical statistical analysis of quantitative data. In our study, initially the transcriptions were searched for

all possible items and factors and also items noted on the flip-over were added to the listed items from the transcriptions. Subsequently, by analyzing these items, main categories were determined and all items were classified into a main category independently by three investigators. Disagreements were solved in consensus. In this way, bias caused by analyzing and interpreting data was minimized by comparing these independently obtained results. Factors were clustered in subcategories after consensus. Then, the importance of the separate items was assessed by determining the frequency in which they were mentioned. The frequency of an item was used as a proxy for impor-

Physical factors	101 (35.3%)	Patients' expectations or individually determined factors	50 (17.5%)
pain	15	consideration of being operated upon	7
open wound	11	fear of the operation	6
food related complaints	11	an individual's willingness to resume work	4
general physical complaints	11	a person's character	3
change for the better	9	individual differences	2
wound pain	7	recovery is disappointing compared to others	3
diarrhea	6	differences in experiencing pain	2
insomnia	6	experiences in the past	1
shoulder pain	5	other individual circumstances	3
lack of endurance	5	self determination	1
abdominal colic's	5	scar	4
gastrointestinal complaints	4	nervous disposition	2
infection	3	relaxed attitude	3
tiredness	3	disappointing	3
		fear for resuming work activities	1
		other	5
Work-related factors	**46 (16.1%)**	**Influence, expectations or advice by thirds**	**24 (8.4%)**
type of work	11	discouraged by others	5
adapted work activities	8	pressure by employer	2
work with lifting activities	6	expectation of company physician	1
part-time work	3	advice of company physician	1
discouraged by employer	3	other factors related to company physician	2
work atmosphere	2	pressure by company physician	1
influence of temperature on wound	2	advice of surgeon	2
possibility to return home early	2	advice of any other physician	1
company physician related	1	financial pressure	1
autonomy	1	structure of health care	1
being in contact with the company	1	society's expectations	1
continuity at work	1	people's expectations	2
no use of a partly recovered colleague	1	advise of others	1
independent (own store)	1	taking others into consideration	1
relation with employer	1	expectations of children	2
other	3		

Table 1: Score of items relating to return to work in patients focus groups.

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tance. After assessing the frequencies of each item, the importance of an individual item as well as the importance of a main group could be determined.

RESULTS

After transcription of the tapes and checking the flip-overs, eight main categories were defined: 'physical', 'hospital stay related', 'home', 'work-related', 'influence or advice (including expectations) of others', 'patients' expectations or individually determined factors', 'information', and 'other'. Consequently, items relating to the same subject were summed, leading to subcategories.

Hospital related factors		47 (16.4%)
	good follow-up care	9
	earlier discharge	5
	delayed discharge	5
	operative technique	5
	operation delay	4
	postoperative information	3
	physicians with limited time	3
	gallbladder condition	3
	visit to outpatients' clinic	3
	anesthesia	3
	operating surgeon dependent	2
	waiting list	1
	changing physicians	1
Home factors		12 (4.2%)
	children	8
	housekeeping	2
	getting bored at home	1
	gender differences	1
Information related factors		6 (2.1%)
Other		0

Patients' focus groups

Results of the patients' focus groups are shown in table 1. All items of the two groups were combined and led to 309 items. A total of 23 items were irrelevant to return to work (e.g. a patient mentioning that it took a long time before the diagnosis was set), resulting in the 286 items that are listed (Table 1). Physical limitations (35.3%), individual patient factors (17.5%), hospital-related factors (16.4%), and work-related factors (16.1%) were important factors in time to return to the job. Influence or advice comprised only 8.4% of the items mentioned in the decision to resume the job. Home factors (4.2%) or information related factors (2.1%) were not experienced by patients to be important reasons for delaying or resuming work activities.

Within the physical factor, pain (14.9%), an open wound (10.9%), food-related

complaints (10.9%), wound complaints (10.9%), and general health related complaints (10.9%) were mentioned most frequently. A reduction in physical complaints after cholecystectomy was mentioned by 8.9% as a positive factor for return to work. Other factors were: wound pain (6.9%), diarrhea (5.9%), and insomnia (5.9%).

In the individual patient factor, patients mentioned that they had to be careful to resume their work as a simple consequence of having surgery (14%). Differences in the type of person (6%) and having fear for the operation (12%) were important reasons as well.

In hospital related factors, patients mentioned a positive follow-up care after the operation (19.1%), earlier (10.6%) or delayed (10.6%) discharge and the type of surgery (10.6%) to be important reasons.

Influence or advice (including expectations) by thirds	55 (21.8%)	Information related factors	54 (21.4%)
society's expectations	10	lack of information	13
structure of health care	8	lack of guidelines	10
advise of others	7*	a structure for communication	9
influences of cultural differences	7	pamphlet information	6
people's expectations	6*	lack of advice	4
advice of general practitioner	6*	positive attitude	3
advice of company physician	4*	differences in interpretation of information	2
advice of surgeon	3*	other	7
employer's expectations	2		
other	2		
Patients' expectations or individually determined factors	35 (13.9%)	Hospital related factors	31 (12.3%)
individual differences	8	information about the operation	8*
a person's character	7	type of operation	7
motivation	5	visit to outpatients' clinic	7*
personal circumstances	5	information on recovery	4*
differences in experiencing pain	3	hospital stay	2
an individual's interpretation of information	2	waiting list	2
other	5	good follow-up care	1
		Home factors	4 (1.6%)

*Table 2: Score of items relating to return to work in physicians focus groups. * items somehow relating to information,*

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In the work related factors, the type of work (23.9%), adapted work (17.4%) and work requiring weight lifting (13%) were most important.

"... initially I assisted in administrative activities, which is completely different from my usual activities on the job ..."

The main category 'influence or advice' was mentioned in 8.4% to be important and within this main category, the influence or advice of a physician was the reason in 33.3%. Sometimes patients wanted to work, but others advised them not to (20.8%).

"... the company physician advised not to resume work and to take it easy, just because I had abdominal surgery ..."

ors	54 (21.4%)	**Work-related factors**	41 (16.3%)
	13	type of work	7
	10	initiatives of the employer	6
cation	9	possibility to return home early	6
	6	work atmosphere	4
	4	motivation	4
	3	adapted work activities	4
ion of information	2	financial aspects employer	3
	7	relation with employer	2
		commitment	2
		independent (own store)	2
		other	1
	31 (12.3%)	**Physical factors**	20 (7.9%)
eration	8*	pain	8
	7	tiredness	6
	7*	diarrhea	2
	4*	endurance	2
	2	wound healing	2
	2		
	1		
		Other	12 (4.8%)
	4 (1.6%)	legal aspects	4
		analgesics	4
		other	4

how relating to information,

not scored in the information category.

Physicians focus groups

Results of the physicians' focus groups are shown in table 2. All items of these two groups were combined and led to 280 items. A total of 28 items were irrelevant to return to work (e.g. someone describing situations in other countries), resulting in the 252 items that are listed (Table 2). Influence or advice by others (21.8%) and information-related factors (21.4%) were the two most important categories in time to return to the job in the physicians' groups. Work-related factors (16.3%), individual patient factors (13.9%) and hospital-related factors (12.3%) were assessed less important in the decision to return to work. Physical factors (7.9%) and home factors (1.6%) were not experienced by physicians to be important reasons for patients in delaying or resuming their work activities.

Within the 'influence or advice by others' category, physicians assessed that society expectations were the most important subcategory (18.2%). The structure of health care and financial arguments was thought to be important as well (14.5%). Other factors that were revealed: advices in general (12.7%), the role of the general practitioner (10.9%) and advices by societal contacts of patients (like neighbors) (10.9%). Cultural factors were thought to be important as well (12.7%).

In the (secondly most important) 'information-related items' category, physicians thought that lack of information (on expectations) to the patient is mainly responsible for delay in return to work (24.1%). Additionally, supplying information to patients by a pamphlet (11.1%) and a lack of guidelines (18.5%) were thought to be important as well.

"... do company physicians have guidelines on what to advice to patients considering the moment to return to work? No. And do general practitioners have guidelines? No. In the surgical world there are no guidelines or evidence on when to return to work either ... Actually, nobody knows what should be advised to patients ..."

Another important and time consuming issue in the discussions (and all physicians agreed on being important) was the lack of a structure to communicate between surgeons, general practitioners and company physicians (16.7%).

"... There is no contact and communication between surgeons, general practitioners and company physicians on what to advice to a patient on return to work. A structure for communication is necessary and currently missing, especially quick communication ..."

In the work-related category, the type of work (17.1%), initiative by the employer to contact the employee (14.6%), and flexibility (24.4%) (including adaptive activities (9.8%) and possibilities to return home at all times (14.6%)) were assessed important in the decision of patients to resume activities. Additionally the atmosphere at the job (9.8%) and an individual's motivation (9.8%) were assessed by physicians to play a role.

In the individual patient factors category, individual factors (22.9%), personality (20%), an individual's motivation (14.3%) and specific individual circumstances (14.3%) were the main subcategories.

In the hospital related category, physicians assessed that patients being informed by surgeons about operative findings (25.8%) and the process at the outpatients' clinic (22.6%) were the main subcategories. The type of operative technique (22.6%) was thought to be important as well.

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DISCUSSION

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Summarizing all items somehow relating to information or advice (including lack of information, lack of advice and incorrect advice), lead to a total of 99 items (39.3%).

DISCUSSION

The aim of our study was to retrieve a wide range of aspects that influence the moment of return to work after cholecystectomy and we hypothesized that a physicians' advice would be important in the decision when to return to the job. This qualitative research showed that physicians believe that their advices are most important. In contrast, patients mentioned this factor seldom and experience physical complaints as the major reason influencing their return to work. The hypothesis was rejected that a physicians' advice was important in a patients' decision to return to work. Our study showed that we need to pay more attention to the physical complaints after cholecystectomy. Surprisingly, guidelines concerning advice when to resume work activities and communication between physicians appear to be missing. Structured communication between physicians may supply the patient with an individual appropriate advice.

It has to be emphasized that we used a qualitative design and results should therefore be considered in an explorative perspective. Drawing quantitative conclusions from this study is inappropriate.

The inclusion criterion that patients had their cholecystectomy at least six months earlier may very well have resulted in recall bias. However, it was considered that a shorter period might have distorted results by information bias as a consequence of differences in the state of recovery in the participating patients. Patients might very well have overestimated the importance of current factors compared to factors that played a role in the past. Overall, we had the impression that patients remembered their recovery and sick-leave very well.

As far as we know, in literature only the influence of specific factors on the moment of return to the job was evaluated [12-15]. No attempt has been made thus far to identify a wide range of factors that influence the moment back to work. The factor 'an older age' was not identified, but all other factors mentioned in literature were included in our results. Work incapacity before the intervention was not the focus of this study.

We found several discordant findings between the patients and physicians focus groups. The first most striking difference between patients and physicians was that physicians think their advice is most important. Most of the items in the physicians group concerned

advices to a patient to resume work. These physician advices were not mentioned in the patient group and, thus, time back to work is not related to this. There were some other items concerning possibilities of physicians believing that in some way the recovery of patients after surgery could be influenced (e.g. by preoperative expectations). Obviously, patients would not mention these items while they were not aware of the possibilities how their recovery could be influenced. This partly explained the difference between the two types of groups. It was also remarkable that some patients wanted to resume work, but they were advised by company physicians not to do so. Apparently, physicians were sometimes too careful.

Another major discordance was found in physical factors. Patients experienced physical complaints as the most important reason causing delay in return to work, while physicians did not assess the physical factors to be important. One could expect that pain in some way inhibits patients' return to work, but more surprising was the large number of gastro-intestinal complaints. Inability to eat, intestinal colic's and a disturbed defecation (i.e. diarrhea) were frequently mentioned reasons not to return to work. Being tired, inability to sleep and lack of general fitness were also frequently mentioned. A reduction in physical complaints after cholecystectomy was mentioned seldom by patients as a positive factor, while one would expect that disappearance of symptomatic cholecystolithiasis would be an important positive reason for resuming work activities.

Another problem that became obvious in the physicians groups concerned communication between various types of physicians. There appeared to be no communication between surgeons, general practitioners and company physicians relating to the moment of return to work of a patient. Company physicians sometimes wanted to ask a surgeon for advice, but writing, sending, answering, and returning a letter takes up too long (several weeks) and was, therefore, impractical. Making a phone call often was a problem as well (e.g. because of performing surgery). In future, communication between surgeons and company physicians could combine technical information of the operation with the specific work-related knowledge of company physicians and might result in an appropriate advice for the individual patient.

One of the most surprising remarks in the physicians' groups came up when the existence of protocols was discussed. Each type of physician thought that the others had some kind of protocol about a standard period of sick leave and expected that their colleagues advised patients on when to return to work. However, no protocol or guidelines existed and no concrete advice was given to the patient. The main thing physicians told their patients in relation to time back to work was to listen to their body and to return to the job as soon as they felt well enough to do so. Advices varied and it seemed that every physician generates his or her own advice independent from each other. Company

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physicians and general practitioners gave advices without asking a surgeon for his opinion and a surgeon usually did not give any advice or simply referred to the company physician.

Since we included patients with a paid job in our focus group discussions it is not possible to conclude from our study on convalescence in patients without a paid job, although some factors might very well apply to these patient categories as well. We focused on individual aspects using a qualitative study design. The influence of other, non individual, more general factors like differences in social class and education level should be addressed by a quantitative study design.

This raises the question whether our results are generalisable to other general surgical procedures such as inguinal hernias, appendectomies and varicose surgery. We feel that many factors may very well be generalisable. Alternatively, other factors and especially incentives in the health care system may vary considerably from one place to another. The results may be different in countries without a Western European social security system where patients suffer financial loss during sick leave. Financial situations are different and the factors influencing return to work may therefore differ as well. However, future research is necessary to examine this.

CONCLUSION

Physicians perceive of their advices as an important factor in patients' duration of sick leave. In contrast, patients seldom mention this factor and experience physical complaints as the major reason influencing the moment of return to work.

Attention has to be paid to patients' physical complaints after cholecystectomy as well as to the way information is supplied to the patient. More adequate information, generating guidelines on time back to work in general and improving communication between types of physicians, might result in an appropriate advice for every individual patient. Knowledge of factors influencing the moment of return to work may result in improvements of patients' recovery. Additionally, reductions in sick-leave and subsequently substantial savings in indirect costs may be reached.

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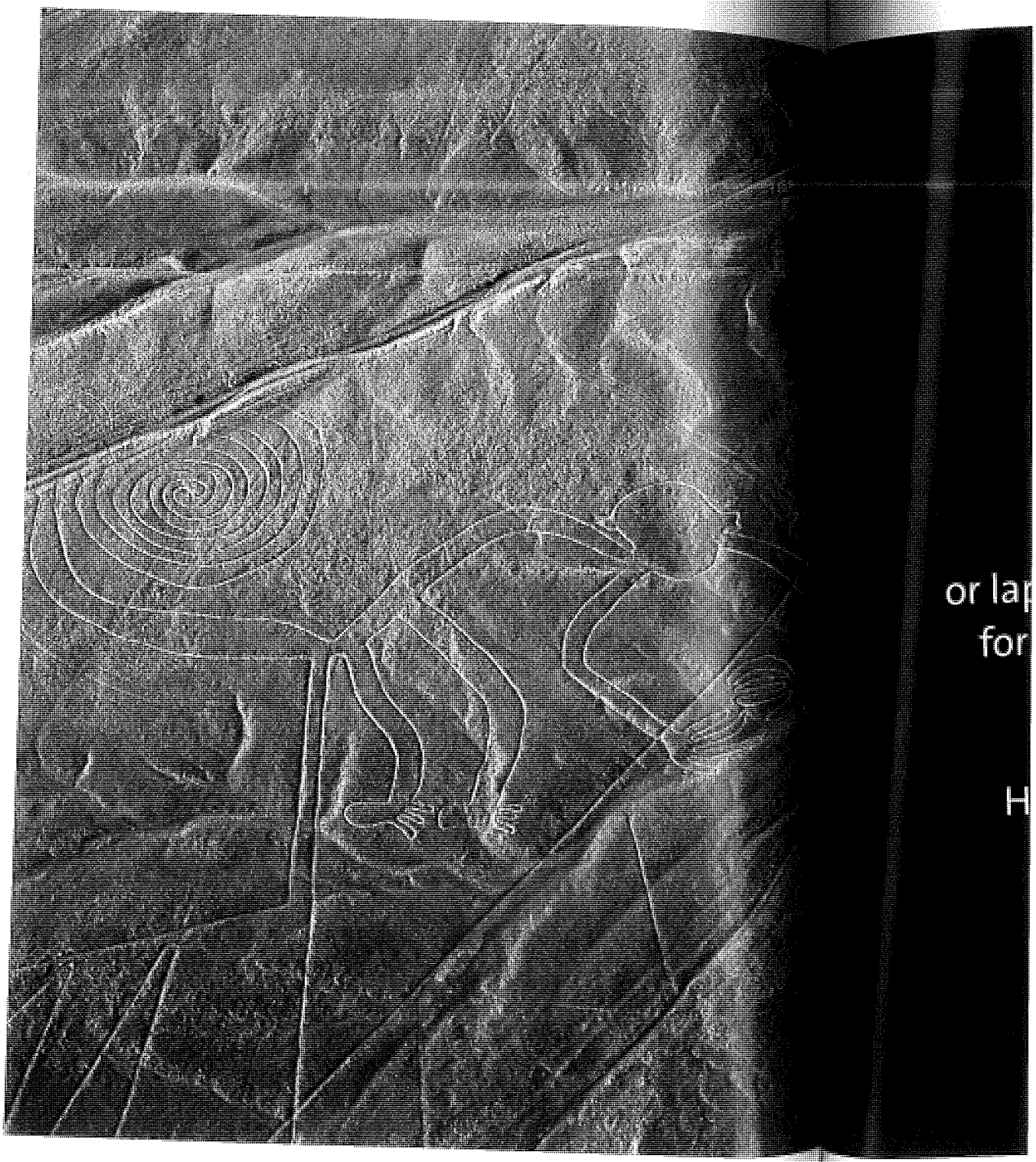

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Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews

F. Keus, H. G. Gooszen, C. J. H. M. van Laarhoven

Cochrane Database Syst Rev 2010; Issue 1:CD008318

ABSTRACT

Background

Patients with symptomatic cholecystolithiasis are treated by three different techniques of cholecystectomy: open, small-incision, or laparoscopic. There is no overview on Cochrane systematic reviews on these three interventions.

Objectives

To summarise Cochrane reviews that assess the effects of different techniques of cholecystectomy for patients with symptomatic cholecystolithiasis.

Methods

The Cochrane Database of Systematic Reviews (CDSR) was searched for all systematic reviews evaluating any interventions for the treatment of symptomatic cholecystolithiasis (Issue 4, 2009).

Main results

Three systematic reviews that included a total of 56 randomised trials with 5246 patients are included in this overview of reviews. All three reviews used identical inclusion criteria for trials and participants, and identical methodological assessments.

Laparoscopic versus small-incision cholecystectomy

Thirteen trials with 2337 patients randomised studied this comparison. Bias risk was relatively low. There was no significant difference regarding mortality or complications. Total complications of laparoscopic and small-incision cholecystectomy were high, i.e., 17.0% and 17.5%. Total complications (risk difference, random-effects model -0.01 (95% confidence interval (CI) -0.07 to 0.05)), hospital stay (mean difference (MD), random-effects -0.72 days (95% CI -1.48 to 0.04)), and convalescence were not significantly different. Trials with low risk of bias showed a quicker operative time for small-incision cholecystectomy (MD, low risk of bias considering 'blinding', random-effects model 16.4 minutes (95% CI 8.9 to 23.8)) while trials with high risk of bias showed no statistically significant difference.

Laparoscopic versus open cholecystectomy

Thirty-eight trials with 2338 patients randomised studied this comparison. Bias risk was high. Laparoscopic cholecystectomy patients had a shorter hospital stay (MD, random-effects model -3 days (95% CI -3.9 to -2.3)) and convalescence (MD, random-effects model -22.5 days (95% CI -36.9 to -8.1)) compared with open cholecystectomy but did not differ significantly regarding mortality, complications, and operative time.

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Seven trials with 571 patients randomised studied this comparison. Bias risk was high. Small-incision cholecystectomy had a shorter hospital stay (MD, random-effects model -2.8 days (95% CI -4.9 to -0.6)) compared with open cholecystectomy but did not differ significantly regarding complications and operative time.

Authors' conclusions

No statistically significant differences in the outcome measures of mortality and complications have been found among open, small-incision, and laparoscopic cholecystectomy. There were no data on symptom relief. Complications in elective cholecystectomy are high. The quicker recovery of both laparoscopic and small-incision cholecystectomy patients compared with patients on open cholecystectomy justifies the existing preferences for both minimal invasive techniques over open cholecystectomy. Laparoscopic and small-incision cholecystectomies seem to be comparable, but the latter has a significantly shorter operative time, and seems to be less costly.

PLAIN LANGUAGE SUMMARY

Open, small-incision, and laparoscopic cholecystectomy seem comparable with regard to mortality and complications

Gallstones are one of the major causes of morbidity in western society. Prevalence of persons with asymptomatic and symptomatic gallstones varies between 5% and 22%. There is consensus that only patients with symptomatic gallstones need treatment. Three different operation techniques for removal of the gallbladder exist: the classical open operation technique and two minimally invasive procedures, the laparoscopic and the small-incision technique. This overview evaluates the three surgical procedures and comprises fifty-six trials with 5246 patients randomised.

Complication proportions in all three techniques are high, but there seem to be no significant differences in mortality and complications between the three operation techniques. Both minimally invasive techniques have advantages over the open operation considering postoperative recovery. This overview of three Cochrane Hepato-Biliary Group systematic reviews shows that the laparoscopic and the small-incision operation should be considered equal regarding patient-relevant outcomes (mortality, complications, hospital stay, and convalescence). Operative time seems to be quicker and costs seem to be lower using the small-incision technique.

The question today is why the laparoscopic cholecystectomy has become the standard treatment of cholecystectomy for patients with symptomatic cholecystolithiasis without the evidence being present. We were unable to find any arguments supporting the 'gold standard' status of laparoscopic cholecystectomy.

In future trials, research should concentrate more on outcomes that are relevant to patients (e.g., complications and symptom relief). Furthermore, the execution of the trials should comply with CONSORT requirements (www.consort-statement.org).

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BACKGROUND

Gallstones are one of the major causes of morbidity in western society. In many persons gallstones remain asymptomatic. Treatment is required only in persons with symptomatic gallstones [NIH Consensus conference 1993]. Prevalence of persons with asymptomatic and symptomatic gallstones varies between 5% and 22% in the USA, and the total estimated number of people with gallstones is 20 million (based on 290 million inhabitants) [Legorreta 1993; Everhart 1999]. Prevalence of persons with asymptomatic and symptomatic gallstones in Europe shows similar distributions varying between 25 and 50 million persons (based on 500 million inhabitants in 32 countries) [Jensen 1991; Attili 1995]. It is estimated that the yearly incidence of symptomatic cholecystolithiasis is up to 2.2 per thousand inhabitants [Steiner 1994].

Description of the condition

There is general agreement supported by limited evidence that gallstone carriers with vague symptoms should not undergo cholecystectomy, whereas gallstone carriers with one or more biliary colic should be offered operation [Scott 1992; NIH Consensus conference 1993; Neugebauer 1995]. A biliary colic is typically defined by severe pain in the epigastrium or the right hypochondrium, eventually radiating to the back, persisting for one to five hours, often waking the patient during the night, and sometimes provoked by meals. Classically, patients experience the need to move around, and there is no typical sign at physical examination. The presence of gallstones is usually confirmed by ultrasound examination [Johnston 1993].

Description of the interventions

Cholecystectomy is the preferred treatment in symptomatic cholecystolithiasis and is one of the most frequently performed operations. The annual number of cholecystectomies in the USA exceeds 500,000 patients [Olsen 1991; NIH Consensus conference 1993; Roslyn 1993]. Until the late 1980s, the classical open cholecystectomy was the gold standard for treatment of symptomatic cholecystolithiasis [Traverso 1976]. In the early 1970s, small-incision cholecystectomy was introduced as a minimal invasive procedure [Dubois 1982; Goco 1983]. As incisions for cholecystectomy were shortened, morbidity and complications seemed to decline [Dubois 1982; Goco 1983] and patients recovered faster. Laparoscopic cholecystectomy was first performed in 1985 [Mühe 1986] and rapidly became the method of choice for surgical removal of the gallbladder [NIH Consensus conference 1993], although the evidence of superiority over small-incision cholecystectomy was absent. This rising popularity was based on assumed lower morbidity and complication proportions, and a quicker postoperative recovery compared to open cholecystectomy. Laparoscopic cholecystectomy seemed superior to open cholecystectomy [Deziel 1993; Downs 1996; Shea 1996] and to small-incision cholecystectomy

[Ledet 1990; O'Dwyer 1990; Olsen 1993; Tyagi 1994; Seale 1999]. However, the mentioned studies are non-randomised trials, and accordingly they may not provide a fair assessment of the effects of the interventions.

How the intervention might work

Removal of the gallbladder including its content prevents recurrence of colics caused by gallbladder stones. However, patients often do not present with the classical symptoms of biliary colics. Therefore, patients with non-classical symptoms or asymptomatic gallstones may be offered gallbladder removal in the presence of symptoms originating from other abdominal organs. In fact, abdominal complaints wrongly attributed to co-existent gallstones could explain the relatively high proportions of failures in symptom relief by cholecystectomy.

Why it is important to do this overview

Laparoscopic cholecystectomy is the treatment of choice by consensus in patients with symptomatic cholecystolithiasis [NIH Consensus conference 1993], while high level evidence for this consensus is lacking. Recently, three Cochrane Hepato-Biliary Group systematic reviews have been conducted comparing different surgical techniques for gallbladder removal in these patients [Keus 2006a; Keus 2006b; Keus 2006c]. An overview of the reviews considering the surgical treatment of symptomatic cholecystolithiasis is lacking. This was the reason for preparing this overview of systematic reviews.

OBJECTIVES

The objective was to evaluate the beneficial and harmful effects of different types of cholecystectomy for patients with symptomatic cholecystolithiasis. We wanted to assess whether laparoscopic, small-incision, or open cholecystectomy are different in terms of primary outcomes (mortality, complications, and relief of symptoms) or secondary outcomes (conversions to open cholecystectomy, operative time, hospital stay, and convalescence). When data were available, differences in other secondary outcomes like analgesic use, postoperative pain, pulmonary function, and costs were also compared.

METHODS

The overview was conducted according to the recommendations by *The Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2008] and the *Cochrane Hepato-Biliary Group Module* [Gluud 2009].

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Criteria for considering reviews for inclusion

Only Cochrane reviews were considered for inclusion in this overview. Non-Cochrane reviews were not planned to be included in this overview.

Participants

Participants in the included reviews were patients suffering from symptomatic cholecystolithiasis. Reviews on participants with acute cholecystitis were excluded from this overview for reasons of heterogeneity in patient populations.

Interventions

Only surgical treatments for symptomatic cholecystolithiasis were considered. Three different techniques for cholecystectomy were recognised: open, small-incision, and laparoscopic cholecystectomy. The following classifications of the surgical procedures (based on intention-to-treat) were used:

Laparoscopic cholecystectomy includes those procedures that are started as a laparoscopic procedure; i.e., any kind of laparoscopic cholecystectomy with creation of a pneumoperitoneum (by Veress needle or open introduction) or mechanical abdominal wall lift, irrespective of the number of trocars used.

Only if 'small-incision', 'minimal access', 'minilaparotomy', or similar terms as intended terms were mentioned in the primary classification of the procedure, then the surgical intervention was classified as a 'small-incision' cholecystectomy (i.e., length of incision less than 8 cm). The incision length of up to 8 cm was chosen arbitrarily as most authors had used this length as a cut-off point between small-incision and (conversion to) open cholecystectomy.

All other surgical interventions for gallbladder removal were classified as 'open cholecystectomy'; this traditional procedure can be carried out through a larger, i.e., > 8 cm, subcostal incision or median laparotomy.

Outcomes of interest

Both primary and secondary outcome measures were considered. Primary outcome measures were mortality, complications (including subcategories), and symptom relief. Secondary outcome measures were all other, less important, outcome measures evaluated, if any. All outcomes reported in the three systematic reviews were included.

Search methods for identification of reviews

As only Cochrane reviews were considered for inclusion in this overview of reviews, *The Cochrane Database of Systematic Reviews* (CDSR), Issue 4, 2009, was searched

(Table 1). The systematic reviews had to evaluate any surgical interventions for the treatment of symptomatic cholecystolithiasis. The term 'cholecystectomy' was entered and restricted to title, abstract, or keywords. As describing an operation of the gallbladder in medical terms without the word cholecystectomy is impossible, a maximal sensitive search with the term cholecystectomy was achieved. No other databases were searched. No restrictions in the inclusion criteria of the identified reviews were applied regarding participants, details of the interventions, or outcomes of interest.

Data collection and analysis

The following methods on data collection and data analyses were used in the overview of reviews.

Selection of reviews

The selection process of Cochrane reviews was performed based on the criteria for considering reviews for inclusion. Cochrane reviews were included when comparisons were made between any kind of surgery in patients suffering from symptomatic cholecystolithiasis.

Data extraction and management

Data from the Cochrane reviews were extracted independently by two authors and regarding outcomes not reported in the reviews by one author (FK). Disagreements were resolved by consensus. In case of missing data, all original reports of included trials were assessed and additional analyses of missing data were performed if appropriate.

Assessment of methodological quality of included reviews

Quality of included reviews

The quality of the included reviews was taken into account. We described the quality of the reviews in a narrative way. The risk of systematic errors (bias) in systematic reviews is influenced by the risks of systematic errors (bias) in the primary trials included in the systematic review.

Quality of evidence in included reviews

Only recently, methodological quality assessment is recommended according to the

Database	Search performed in	Search strategy
The Cochrane Database of Systematic Reviews (CDSR)	Issue 4, 2009	'cholecystectomy'

Table 1: Search strategy

Review | Date assessed as up to date | Population | Interventions | Comparison interventions | Outcomes for which data were reported | Review limitations

Review	Date assessed as up to date	Population	Interventions	Comparison interventions	Outcomes for which data were reported	Review limitations
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Small-incision cholecystectomy	Open cholecystectomy	Primary: complications Secondary: operative time, hospital stay	Systematic error: the included trials had relatively low methodological quality Random error: only 7 trials including 572 patients were included Time: the review needs updating
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Laparoscopic cholecystectomy	Open cholecystectomy	Primary: mortality, complications Secondary: operative time, hospital stay, convalescence	Systematic error: the included trials had relatively low methodological quality Time: the review needs updating
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	Searches were performed in 2004 Review published in 2006	Patients with symptomatic cholecystolithiasis	Laparoscopic cholecystectomy	Small-incision cholecystectomy	Primary: mortality, complications Secondary: conversions, operative time, hospital stay, convalescence	Time: the review needs updating

Table 2: Characteristics of included reviews

Search strategy

'cholecystectomy'

GRADE recommendations [Atkins 2004; Atkins 2005; Guyatt 2008; Guyatt 2008a]. However, the quality of evidence of the included trials in the reviews, prior to this new assessment tool, was assessed according to four components assessing risk of bias: generation of the allocation sequence, allocation concealment, blinding, and follow-up. We described the bias risk of the included trials as they were assessed in the included reviews.

Data synthesis

Data were extracted from the underlying systematic reviews, and the summary findings were presented in tables (Table 2; Table 3; Table 4; Table 5; Table 6; Table 7). Data were extracted from direct comparisons, and no indirect comparisons were made since evidence from indirect comparisons may be less reliable than evidence from direct (head-to-head) comparisons. All data rest on intention-to-treat analyses.

RESULTS

A total of 14 systematic reviews were identified by the search strategy in the Cochrane Database of Systematic Reviews. Three of these systematic reviews could be included (Table 2) [Keus 2006a; Keus 2006b; Keus 2006c]. For detailed descriptions of all results, we refer to the three individual Cochrane Hepato-Biliary Group reviews [Keus 2006a; Keus 2006b; Keus 2006c] and a paper publication in which all the three reviews were updated [Keus 2008a].

Description of included reviews

The included three reviews contain a total of 56 randomised trials with 5246 patients randomised. One of the randomised trials [Coelho 1993] was included in all the three systematic reviews because it had three parallel-group comparisons [Keus 2006a; Keus 2006b; Keus 2006c].

The *Cochrane Database of Systematic Reviews* in *The Cochrane Library* (Issue 4, 2009) was searched to identify reviews for this overview of reviews. The three systematic reviews used identical inclusion criteria for inclusion of trials. Only randomised trials were included. Identical criteria for types of participants were used. Three reviews were included which compared open, small-incision, and laparoscopic cholecystectomy (Table 2).

Identical outcome measures were considered in the three systematic reviews [Keus 2006a; Keus 2006b; Keus 2006c]. Primary outcomes were distinguished from secondary outcome measures (Table 3; Table 4). Primary outcomes were mortality and complications. Complications were subcategorised into four subcategories (intra-operative,

Review	Mortality	Intra-operative complications	Minor complications	Severe complications	Bile duct injuries	Total complications
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Review		Mortality	Intra-operative complications	Minor complications	Severe complications	Bile duct injuries	Total complications
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	0 (0)	571 (7)	571 (7)	571 (7)	571 (7)	571 (7)
	Trials with low risk of bias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	987 (15)	1914 (30)	1914 (30)	1914 (30)	1914 (30)	1914 (30)
	Trials with low risk of bias	0 (0)	63 (2)	63 (2)	63 (2)	63 (2)	63 (2)
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	1952 (7)	2315 (12)	2315 (12)	2315 (12)	2315 (12)	2315 (12)
	Trials with low risk of bias	1181 (3)	1181 (3)	1181 (3)	1181 (3)	1181 (3)	1181 (3)

Table 3: Overview of primary outcomes: numbers of included patients and trials.

The three rows represent the three included reviews. The outcomes are in the columns, including all patients and all trials and separately for the trials with low risk of bias. The numbers in the columns are the numbers of randomised patients with the numbers of trials reporting that outcome in brackets.

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Review		Conversions	Convalescence: work leave (days)	Convalescence: normal activity (days)	Operative time (minutes)	Hospital stay (days)
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	n.a.	0 (0)	0 (0)	210 (3)	180 (2)
	Trials with low risk of bias	n.a.	0 (0)	0 (0)	0 (0)	0 (0)
Open versus laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	n.a.	328 (3)	0 (0)	1134 (24)	1111 (21)
	Trials with low risk of bias	n.a.	0 (0)	0 (0)	20 (1)	20 (1)
Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	2132 (8)	1181 (3)	1158 (4)	1953 (9)	1614 (8)
	Trials with low risk of bias	1181 (3)	1181 (3)	924 (2)	1181 (3)	1181 (3)

Table 4: Overview of secondary outcomes: numbers of included patients and trials.

n.a. not available. The three rows represent the three included reviews. The outcomes are in the columns, including all patients and all trials and separately for the trials with low risk of bias. The numbers in the columns are the numbers of randomised patients with the numbers of trials reporting that outcome in brackets.

Review		Conversions	Convalescence: work leave (days)	Convalescence: normal activity (days)	Operative time (minutes)	Hospital stay (days)
Open versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis	*All trials*	n.a.	0 (0)	0 (0)	210 (3)	180 (2)
	Trials with low risk of bias	n.a.	0	0	0	0

bile duct injuries, minor complications, and severe complications) apart from total complication proportions. Secondary outcomes were convalescence (including return to normal activity and return to work), operative time, and hospital stay. No data were available considering symptom relief.

Methodological quality of included reviews

The methodological quality of the randomised clinical trials in the included reviews was evaluated by assessing the following risk of bias components: generation of the allocation sequence, allocation concealment, blinding, and follow-up [Higgins 2006; Gluud 2009]. Each component was assessed adequate, unknown ('not performed' for blinding), or inadequate. Subgroup analyses were performed based on these assessments. The risk of bias of the included trials was considered high both in the small-incision versus open cholecystectomy and in the laparoscopic versus open cholecystectomy comparisons, while it was considered relatively low in the laparoscopic versus small-incision cholecystectomy comparison.

Effect of interventions - Outcomes reported in the systematic reviews

Summary of findings were reported in Table 5, Table 6, and Table 7.

Mortality

Mortality was not reported in all seven trials in the small-incision versus open cholecystectomy comparison. Mortality was reported in 14 trials in the laparoscopic versus open cholecystectomy comparison and in seven trials in the laparoscopic versus small-incision cholecystectomy comparison.

We found no significant differences in mortality between the three techniques. Mortality rates were low (up to 0.09%) in the different comparisons.

Complications

Complications were categorised into intra-operative, minor, severe, bile duct injury complications, and total complication proportions. There were no significant differences in any of the complication categories.

Intra-operative complications

There were zero intra-operative complications in the small-incision versus open cholecystectomy comparison. In the laparoscopic versus open cholecystectomy comparison, the intra-operative complication proportions were 0.9% and 0.1%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the intra-operative complications were 13.1% and 7.6%, respectively.

We found no significant differences in the intra-operative complications between the three techniques.

Minor complications

In the small-incision versus open cholecystectomy comparison, the minor complication proportions were 8.6% and 6.8%, respectively. In the laparoscopic versus open cholecystectomy comparison, the minor complication proportions were 2.1% and 3.1%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the minor complications were 8.3% and 9.2%, respectively.

We found no significant differences in the minor complications between the three techniques.

Severe complications

In the small-incision versus open cholecystectomy comparison, the severe complication proportions were 1.4% and 2.5%, respectively. In the laparoscopic versus open cholecystectomy comparison, severe complication proportions were 2.2% and 6.8%, respectively, and in the laparoscopic versus small-incision cholecystectomy comparison, the severe complications were 4.0% and 4.2%, respectively.

		Quality assessment				
Outcomes		Limitations	Inconsistency	Indirectness	Imprecision	Other
Intraoperative complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none
Minor complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none
Severe complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none
Bile duct injuries	All trials	very serious	serious	no serious indirectness	serious	none
Total complications	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none

Table 5: Summary of Findings table: OC vs SIC.

*Modified table using GRADE pro software. OC: open cholecystectomy; SIC: small-incision cholecystectomy; RR: relative risk. GRADE Working Group grades of evidence: **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*

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We found no significant differences in the severe complications between the three techniques.

Bile duct injury

In the small-incision versus open cholecystectomy comparison, zero bile duct injuries were reported. In the laparoscopic versus open cholecystectomy comparison, the proportion of bile duct injuries was 0.2% in both groups. In the laparoscopic versus small-incision cholecystectomy comparison, the bile duct injury proportions were 1.2% and 1.9%, respectively (risk difference, fixed-effect model -0.01, 95% CI -0.02 to 0.00). The difference is mainly caused by eight patients with bile leakage with unknown origin and conservative treatment in the small-incision group (five patients from one trial).

We found no significant differences in the bile duct injuries between the three techniques.

Total complications

In the small-incision versus open cholecystectomy comparison, no significant differences were found; the total complication proportions were 9.9% and 9.3%, respectively (risk difference 0.00, 95% CI -0.06 to 0.07).

ectness	Imprecision	Other	Summary of findings Risk OC (control)	Risk SIC (comparator)	Relative effect SIC vs OC	Absolute effect SIC vs OC	Quality of the evidence (GRADE)
rious ectness	serious	none	0 per 279 (0%)	0 per 292 (0%)	not estimable	0 more per 1000	VERY LOW
rious ectness	serious	none	19 per 279 (6.8%)	25 per 292 (8.6%)	1.26	18 more per 1000	VERY LOW
rious ectness	serious	none	7 per 279 (2.5%)	4 per 292 (1.4%)	0.56	11 fewer per 1000	VERY LOW
rious ectness	serious	none	0 per 279 (0%)	0 per 292 (0%)	not estimable	0 fewer per 1000	VERY LOW
rious ectness	serious	none	26 per 279 (9.3%)	29 per 292 (9.9%)	1.06	6 more per 1000	VERY LOW

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Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of five factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias. Upgrading of evidence (increase quality of evidence) may occur based on the assessment of three factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

In the laparoscopic versus open cholecystectomy comparison, the total complication proportions were 5.4% and 10.1%, respectively. Although significant differences were found including all trials and in the trials with high risk of bias (risk difference -0.04, 95% CI -0.07 to -0.01), no significant difference was found in the trials with low risk of bias (risk difference -0.01, 95% CI -0.05 to 0.02).

No significant differences were observed in the total complication proportions in the

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		Quality assessment					Summa
Outcomes		Limitations	Inconsistency	Indirectness	Imprecision	Other	Risk OC (contro
Mortality	All trials	very serious	no serious inconsistency	no serious indirectness	serious	none	1 per 4 (0.2%)
Intraoperative complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	1 per 9 (0.1%)
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	0 per (0%)
Minor complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	35 per (3.7%)
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	1 per (3.1%)
Severe complications	All trials	very serious	serious	no serious indirectness	serious	none	72 pe (7.7%
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	1 per (3.1%
Bile duct injuries	All trials	very serious	serious	no serious indirectness	serious	none	2 pe (0.2
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	very serious	none	0 pe (0%
Total complications	All trials	very serious	serious	no serious indirectness	no serious imprecision	none	110 (11.7
	Trials with low risk of bias	serious	no serious inconsistency	no serious indirectness	serious	none	2 p (6.

Table 6: Summary of Findings table: OC vs LC

Modified table using GRADE pro software. OC: open cholecystectomy; LC: laparoscopic cholecystectomy; RR: relative risk GRADE Working Group grades of evidence: ***High quality:*** *Further research is very unlikely to change our confidence in the estimate of effect.* ***Moderate quality:*** *Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*

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laparoscopic versus small-incision cholecystectomy comparison (26.6% and 22.9%, respectively) (risk difference -0.01, 95% CI -0.07 to 0.05) with 1.6% re-operations in both groups. We also summarised the complications in trials, in which three or more bias components were considered adequate. There was no significant difference in the proportions of total complications between laparoscopic and small-incision cholecystectomy when only trials with low risk of bias were included. However, in the trials with low risk of bias the complication proportions in both groups were higher than the

Summary of findings

ectness	Imprecision	Other	Risk OC (control)	Risk LC (comparator)	Relative effect LC vs OC	Absolute effect LC vs OC	Quality of the evidence (GRADE)
:rious ectness	serious	none	1 per 485 (0.2%)	0 per 502 (0%)	not estimable	2 fewer per 1000	VERY LOW
:rious ectness	no serious imprecision	none	1 per 939 (0.1%)	9 per 975 (0.9%)	9.0	8 more per 1000	VERY LOW
:rious ectness	serious	none	0 per 32 (0%)	0 per 31 (0%)	not estimable	0 more per 1000	LOW
:rious ectness	no serious imprecision	none	35 per 939 (3.7%)	23 per 975 (2.4%)	0.65	13 fewer per 1000	VERY LOW
:rious ectness	serious	none	1 per 32 (3.1%)	0 per 31 (0%)	not estimable	31 fewer per 1000	LOW
:rious ectness	serious	none	72 per 939 (7.7%)	25 per 975 (2.6%)	0.34	51 fewer per 1000	VERY LOW
:rious ectness	serious	none	1 per 32 (3.1%)	0 per 31 (0%)	not estimable	31 fewer per 1000	LOW
:rious rectness	serious	none	2 per 939 (0.2%)	2 per 975 (0.2%)	1.0	0 fewer per 1000	VERY LOW
:rious rectness	very serious	none	0 per 32 (0%)	0 per 31 (0%)	not estimable	0 fewer per 1000	VERY LOW
:rious rectness	no serious imprecision	none	110 per 939 (11.7%)	59 per 975 (6.1%)	0.52	56 fewer per 1000	VERY LOW
:rious rectness	serious	none	2 per 32 (6.3%)	0 per 31 (0%)	not estimable	63 fewer per 1000	LOW

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Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.
The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of 5 factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias.
Upgrading of evidence (increase quality of evidence) may occur based on the assessment of 3 factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

Outcomes		Quality assessment				Other
		Limitations	Inconsistency	Indirectness	Imprecision	
Mortality	All trials	serious	no serious inconsistency	no serious indirectness	serious	none
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	serious	none
Intraoperative complications	All trials	very serious	very serious	no serious indirectness	serious	none
	Trials with low risk of bias	no serious limitations	serious	no serious indirectness	no serious imprecision	none
Minor complications	All trials	serious	serious	no serious indirectness	serious	none
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none
Severe complications	All trials	serious	serious	no serious indirectness	no serious imprecision	none
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none
Bile duct injuries	All trials	serious	serious	no serious indirectness	serious	none
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	serious	none
Total complications	All trials	serious	very serious	no serious indirectness	no serious imprecision	none
	Trials with low risk of bias	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none

Table 7: Summary of Findings table: LC vs SIC

Modified table using GRADE pro software. LC: laparoscopic cholecystectomy; SIC: small-incision cholecystectomy; RR: relative risk. GRADE Working Group grades of evidence: ***High quality:*** *Further research is very unlikely to change our confidence in the estimate of effect.* ***Moderate quality:*** *Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*

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tness	Imprecision	Other	Risk SIC (control)	Risk LC (comparator)	Relative effect LC vs SIC	Absolute effect LC vs SIC	Quality of the evidence (GRADE)
ous tness	serious	none	1 per 977 (0.1%)	1 per 975 (0.1%)	1.00	0 fewer per 1000	LOW
ious ctness	serious	none	0 per 599 (0%)	0 per 582 (0%)	not estimable	0 fewer per 1000	MODERATE
ious ctness	serious	none	88 per 1151 (7.6%)	153 per 1164 (13.1%)	1.72	55 more per 1000	VERY LOW
rious ctness	no serious imprecision	none	87 per 599 (14.5%)	153 per 582 (26.3%)	1.81	118 more per 1000	MODERATE
rious ctness	serious	none	106 per 1151 (9.2%)	97 per 1164 (8.3%)	0.90	9 fewer per 1000	VERY LOW
rious ectness	no serious imprecision	none	58 per 599 (9.7%)	57 per 582 (9.8%)	1.01	1 more per 1000	HIGH
erious rectness	no serious imprecision	none	48 per 1151 (4.2%)	46 per 1164 (4.0%)	0.95	2 fewer per 1000	LOW
erious rectness	no serious imprecision	none	34 per 599 (5.7%)	27 per 582 (4.6%)	0.81	11 fewer per 1000	HIGH
serious irectness	serious	none	22 per 1151 (1.9%)	14 per 1164 (1.2%)	0.63	6 fewer per 1000	VERY LOW
serious irectness	serious	none	10 per 599 (1.7%)	8 per 582 (1.4%)	0.82	3 fewer per 1000	MODERATE
serious irectness	no serious imprecision	none	264 per 1151 (22.9%)	310 per 1164 (26.6%)	1.16	37 more per 1000	VERY LOW
serious irectness	no serious imprecision	none	189 per 599 (31.6%)	245 per 582 (42.1%)	1.33	105 more per 1000	HIGH

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Low quality: *Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.* ***Very low quality:*** *We are very uncertain about the estimate.*
The downgrading in the grades of evidence (decrease quality of evidence) is based on the assessment of 5 factors: limitations in design, inconsistency in results, indirectness of evidence, imprecision of results, and publication bias. Upgrading of evidence (increase quality of evidence) may occur based on the assessment of 3 factors: the magnitude of effect, influence of all residual confounding, and the dose-response gradient.

complication proportions in the trials with high risk of bias.

We found no significant differences in the total complications between the three techniques.

Conversions
Conversion proportions in the small-incision versus open cholecystectomy comparison and in the laparoscopic versus open cholecystectomy comparison have not been reported. No significant differences in conversion proportions were found in the laparoscopic versus small-incision cholecystectomy comparison (13.4% and 16.1%, respectively; risk difference 0.00, 95% CI -0.05 to 0.04).

Operative time
We did not observe significant differences considering operative time in the small-incision versus open cholecystectomy comparison (MD 1.94 minutes, 95% CI -1.37 to 5.25).

We found no significant differences considering operative time in the laparoscopic versus open cholecystectomy comparison (MD 3.79 minutes, 95% CI -4.88 to 12.46).

There is a significant difference in operative time in the laparoscopic versus small-incision cholecystectomy comparison. Small-incision cholecystectomy is significantly faster to perform (MD 9.20 minutes, 95% CI 2.06 to 16.35). Trials with low risk of bias showed significant differences (MD, trials with low risk of bias considering 'blinding', random-effects model 16.4 minutes (95% CI 8.9 to 23.8)), while trials with high risk of bias showed no significant difference.

Hospital stay
In the small-incision versus open cholecystectomy comparison, hospital stay was significantly shorter using the small-incision technique (MD -2.78 days, 95% CI -4.94 to -0.62).

In the laparoscopic versus open cholecystectomy comparison, hospital stay was significantly shorter using the laparoscopic operation (MD -3.07 days, 95% CI -3.89 to -2.26).

In the laparoscopic versus small-incision cholecystectomy comparison, no significant difference regarding hospital stay was present in the trials with low risk of bias (MD, trials with low risk of bias considering 'blinding', random-effects model -0.56 days (95% CI -1.24 to 0.11)), but a significant difference was present in the trials with high risk of bias (MD, trials with high risk of bias considering 'blinding', random-effects model -1.08 days (95% CI -1.88 to -0.28)).

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As convalescence can also be measured according to return to work and return to normal activity (at home), different analyses were conducted.

In the small-incision versus open cholecystectomy comparison, no data were available considering work leave. In the laparoscopic versus open cholecystectomy comparison, a significant difference was found with the laparoscopic cholecystectomy showing a shorter work leave (MD -22.51 days, 95% CI -36.89 to -8.13). In the laparoscopic versus small-incision cholecystectomy comparison, no significant difference between the techniques regarding work leave was found (MD, random-effects model -0.43 days (95% CI -4.37 to 3.51)).

No results were reported in the small-incision versus open cholecystectomy comparison and in the laparoscopic versus open cholecystectomy comparison. Data on convalescence to normal activity were available in the laparoscopic versus small-incision cholecystectomy comparison only: no significant difference was found considering convalescence to normal activity (at home) (MD, trials with low risk of bias considering 'blinding', random-effects model 0.79 days (95% CI -5.96 to 7.55)).

DISCUSSION

Summary of main results

The present overview of three Cochrane Hepato-Biliary Group systematic reviews contains at least nine major findings. First, the comparison of the clinical outcome of open, small-incision, or laparoscopic cholecystectomy has been well tested in 56 randomised clinical trials, and the risk of bias has been relatively low in laparoscopic versus small-incision cholecystectomy trials, but generally high in laparoscopic versus open cholecystectomy trials and in the small-incision versus open cholecystectomy trials. Trials with inadequate methodological components carry a higher risk of bias [Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008]. Second, laparoscopic cholecystectomy does not seem to carry more bile duct injuries than small-incision or open cholecystectomy. In this comparison one has to assume that especially interested and skilled surgeons conducted the trials and carried out the interventions. Therefore, everyday clinical practice and complication rates ought to be followed through clinical databases and compared to benchmark values [Winkel 2007]. Third, the total numbers of patients with complications are high and not significantly different for the three procedures. Fourth, small-incision cholecystectomy takes significantly less time to perform than laparoscopic cholecystectomy. Fifth, both of the minimally invasive techniques have a shorter hospital stay compared with open cholecystectomy. Hospital stay after

laparoscopic and small-incision cholecystectomy was not significantly different. Sixth, convalescence after laparoscopic and small-incision cholecystectomy measured by return to work and return to normal activity was not significantly different. Laparoscopic cholecystectomy shows a shorter convalescence compared with open cholecystectomy. Seventh, there seem to be no significant differences in pulmonary function and analgesic use for laparoscopic and small-incision cholecystectomy (see below). Eighth, there seem to be no significant differences in health status among laparoscopic and small-incision cholecystectomy (see below). Ninth, costs appear to be lower from different perspectives when using the small-incision technique (see below).

Overall, both laparoscopic and small-incision cholecystectomy show quicker convalescence compared with open cholecystectomy. Small-incision cholecystectomy is quicker to perform and associated with lower costs from different perspectives compared with laparoscopic cholecystectomy.

Overall completeness and applicability of evidence

After having conducted the three Cochrane Hepato-Biliary Group reviews, it appeared that both of the minimal-invasive techniques were advantageous compared with the open cholecystectomy. Both minimal-invasive techniques seemed to be comparable. Therefore, we questioned the reliability of our findings of the laparoscopic versus small-incision cholecystectomy review with respect to the primary outcome measures. We performed two additional studies; one assessing the robustness of findings using different pooling methods [Keus 2009a], and the other evaluating the risk of random error [Keus 2009b] by using trial sequential analysis [Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009].

From previous studies including simulation studies, it is known that zero event trials may introduce analytical problems [Sweeting 2004; Bradburn 2007]. In our systematic review there were many zero-event trials. Therefore, we evaluated the role of different continuity corrections, summary effect measures, and statistical methods for pooling data considering outcomes on rare events, including zero event trials. In numerous robustness assessments we found important inconsistencies in inferences, confidence intervals, and pooled intervention effect estimates [Keus 2009a]. An inconsistency in conclusions was found with respect to intra-operative complications. Robustness assessments showed more intraoperative complications in the laparoscopic cholecystectomy group. However, detailed evaluation of the types of intra-operative complication causing this statistical difference showed that intraoperative gallbladder perforations were responsible for this. Many surgeons will not regard gallbladder perforations to be a complication. Therefore, overall, these robustness assessments agreed that no significant difference was found in primary outcomes (mortality and compli-

cations) between

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cations) between laparoscopic and small-incision cholecystectomy.

In another study, we applied trial sequential analysis to our laparoscopic versus small-incision cholecystectomy review [Keus 2009b]. This technique has been developed for the evaluation of the risk of random error due to the play of chance and multiple testing in cumulative meta-analysis in order to prevent premature conclusions due to spurious findings. Analyses were restricted to the primary outcome measures. Additionally we constructed a composite outcome measure 'serious adverse events' including all important complications. Analyses were based on low bias risk estimates of control event rates and intervention effects. Furthermore, adjustments were made for the bias risks of trials as well as heterogeneity. It appeared that the information size needed for strong conclusions is not reached for mortality, bile duct injuries, and severe complications. Considering intra-operative and total complication proportions, it appeared that intraoperative gallbladder perforations influenced the results importantly. After excluding gallbladder perforations from the analyses (for their lack of clinical relevance) the information size needed for strong conclusions was reached. No significant differences were found between laparoscopic and small-incision cholecystectomy considering intraoperative and total complications. Since the more clinical relevant question of potential differences between laparoscopic and small-incision cholecystectomy with respect to serious complications was not answered, we considered the composite outcome measure 'serious adverse events'. The information size needed to draw strong conclusions with respect to serious adverse events is within reach with one additional multicentre trial with low risk of bias. When ignoring intraoperative gallbladder perforations as a complication, all trial sequential analyses agree that so far there is no argument to support either laparoscopic or small-incision cholecystectomy.

Our two additional studies on assessments on robustness of evidence and trial sequential analyses confirm the review conclusions of no significant differences between laparoscopic and small-incision cholecystectomy considering primary outcome measures.

An issue in applicability is the question whether selection for randomised trials introduces bias so that participation is associated with greater risks and that outcomes are worse than expected in daily life practice. Differences in outcomes caused by a different (better or worse) treatment have to be distinguished from a better recording of outcomes. There is empirical evidence that participation in randomised trials does not lead to worse outcomes and that results are applicable to usual practice [Vist 2005; Vist 2008], so there seems to be no difference in treatment outcomes [Winkel 2007]. Yet one could expect that through a more careful follow-up, outcomes are better recorded leading to more objective results.

The three systematic reviews report different complication proportions in both the totals and the complication categories. Complications are higher in the laparoscopic versus small-incision cholecystectomy review compared to the other two reviews. We believe that differences in methodological quality may explain these differences in data: the overall risk of bias in the laparoscopic versus small-incision cholecystectomy review was considered relatively low compared to the other two reviews. These observations are in accordance with other studies showing linkage between unclear and inadequate methodological quality to significant overestimation of beneficial effects and underreporting of adverse effects. High quality trials are more likely to estimate the 'true' effects of the interventions [Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008]. The differences in the design of the trials may also explain differences in complications. Many trials in the laparoscopic versus open cholecystectomy review focus on haemodynamics, acute phase reactants, oxidative stress factor, or endocrine functioning etcetera. These outcomes are short-term results, implying limited follow-up. Moreover, these trials have probably not focused on complications, making registration probably less accurate. Therefore, underreporting may very well explain the lower complication proportions in the laparoscopic versus open cholecystectomy review. However, heterogeneity may be another factor explaining the differences in complication proportions. Other factors like changing practices over the years, changes in surgical techniques, or improvements in anaesthesia cannot be ruled out to play a role as well.

Based on 6 billion people in the world, an occurrence of gallstones of 5%, assuming that 10% of these people become symptomatic, and that roughly 50% of symptomatic patients may undergo cholecystectomy, it can be calculated that 15 million cholecystectomies could be performed worldwide annually. The assumptions are all chosen towards the lower boundaries, so that these calculations probably underestimate the true figure. We showed in the review an average quicker operative time of 16 minutes using the small-incision approach compared with the laparoscopic operation. Accordingly, worldwide, 4 million hours operative time could potentially be saved when changing from laparoscopic to small-incision cholecystectomy annually. Now that resources are becoming scarcer, this may offer additional opportunities and solutions for other problems.

There was no significant difference in hospital stay between laparoscopic and small-incision cholecystectomy, but hospital stay was shorter in both minimally invasive techniques compared with the open cholecystectomy. One might find hospital stay long compared to daily life practice. Probably, study conditions and different practice over time are responsible. Apart from these reasons, there might be other reasons for differences in hospital stay, including cultural differences [Vitale 1991]. However, we have to remember that hospital stay is only a surrogate marker for convalescence and because

of numerous factors influencing its length, it does not necessary reflect objective differences between two operative procedures. Differences in hospital stay in open studies may represent bias, unless the type of surgery is blinded. Therefore, differences in hospital stay have to be interpreted with care. We feel that the importance of hospital stay is overrated in surgical literature, probably due to the fact that it can be measured so easily. The GRADE categorisation of outcomes places hospital stay in perspective to other outcomes like mortality and grades hospital stay as being 'not important for decision making - of lower importance to patients' [Guyatt 2008a]. In case two interventions do not have similar effect on patient important outcomes, length of hospital stay may, however, become important to patients and tax or insurance payers.

Outcomes not reported in the systematic reviews

Additional data are available on other outcomes including pulmonary function and analgesic use, health status, and costs. The conclusions in the individual randomised trials on these outcomes are contrasting. These outcomes were not reported in the systematic reviews and the overview of reviews due to statistical problems in meta-analysing these data as well as a lack of uniformity in the way some of these outcomes were measured. Therefore, we have summarised qualitatively the available data from the randomised trials on these outcomes.

Pulmonary function and analgesic use

Pulmonary function differences between laparoscopic and small-incision cholecystectomy have been studied in seven randomised trials [Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999; Harju 2006; Keus 2007]. Since different variables and different times of measurement were chosen, outcomes were reported inconsistently [Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999; Harju 2006; Keus 2007], involved small numbers of patients [Coelho 1993; Squirrell 1998; Bruce 1999] as well as seemed to incorporate some important methodological shortcomings [Kunz 1992; Coelho 1993; Harju 2006]. Three trials suggested superiority of a procedure, based upon a difference in one [Kunz 1992; Coelho 1993] or two [Bruce 1999] pulmonary function variables. Three trials incorporated sample sizes of 15 patients or less per intervention group [Coelho 1993; Squirrell 1998; Bruce 1999]. Two trials used a blind approach [Squirrell 1998; Keus 2007]. Details on peri-operative anaesthesia management were not provided in five of these trials [Kunz 1992; Coelho 1993; McMahon 1993; McMahon 1994; Squirrell 1998; Bruce 1999]. One larger trial with 64 patients in each group, found that the laparoscopic technique was superior and reported both pulmonary function testing and analgesic use [McMahon 1993; McMahon 1994]. However, this multi-centre trial did not attempt to either blind patients or physicians, details on anaesthesia management were not provided, and an incision of 10 cm was considered small, ignoring the more commonly used 8 cm limitation [McMahon

1993; McMahon 1994]. Harju et al evaluated pulmonary function in some of their patients (without explaining how these were selected) and found no significant difference between both techniques [Harju 2006]. Our trial including 257 patients showed no significant differences evaluating eight pulmonary function variables and analgesic use [Keus 2007]. Overall, qualitatively summarising the results of these seven randomised trials, we conclude that no differences in pulmonary function and analgesic use have been shown between laparoscopic and small-incision cholecystectomy.

Health status

Differences in health status between laparoscopic and small-incision cholecystectomy were examined in four trials [Barkun 1992; McMahon 1994a; Squirrell 1998; Keus 2008b]. Recently, evidence-based guidelines advise to use the gastrointestinal quality of life index (GIQLI) and the short form (SF-36) for evaluating health status in cholecystectomy [Korolija 2004]. Retrospectively, three [Barkun 1992; McMahon 1994a; Squirrell 1998] of the four trials did not use the appropriate questionnaires and one trial did [Keus 2008b]. These questionnaires appear to be valid for evaluating patients' functional recovery after cholecystectomy [Korolija 2004]. One trial with low risk of bias including 257 patients and using the appropriate questionnaires found no significant differences between laparoscopic and small-incision cholecystectomy [Keus 2008b].

Cosmetic results of both minimal-invasive results were evaluated in one trial comparing laparoscopic versus small-incision cholecystectomy [Keus 2008b]. The cosmetic effect of both techniques was evaluated using the validated body image questionnaire [Dunker 1998]. This low bias risk trial did not find any significant difference between laparoscopic and small-incision cholecystectomy in the 257 patients [Keus 2008b].

Costs

Differences in costs between laparoscopic and small-incision cholecystectomy were considered in seven trials [McMahon 1994a; Barkun 1995; Calvert 2000; Srivastava 2001; Secco 2002; Nilsson 2004; Keus 2009c]. There are several problems in analysing and pooling cost results from different studies. First, costs are reported in different ways including different cost items. Second, different points of views are taken making comparison of studies difficult. Generally, a societal perspective is recommended [Siegel 1997; Oostenbrink 2002]. Third, there is a difference in validity of cost assessments, defined by the details in which costs are calculated. More detailed analyses provide more reliable estimates [Graves 2002]. Fourth, there may be considerable differences in local costs. Specific items in cost analyses differ from one country or even setting to another. Fifth, cultural differences are probably the most important problem. There are wide variations in convalescence (and return to work) between different cultures depending on a multitude of causes, like social security and cultural habits [Vitale 1991].

These multiple factors cause heterogeneity, and pooling results seems, therefore, inappropriate. So far, seven trials measured costs, and several of these trials had high risk of bias [McMahon 1994a; Barkun 1995; Srivastava 2001; Secco 2002]. In some trials methodology of cost assessment was very limited described [McMahon 1994a; Srivastava 2001]. Outpatients' costs [Calvert 2000; McMahon 1994a] and indirect costs [McMahon 1994a; Barkun 1995; Calvert 2000; Secco 2002] were excluded in several studies making overall (societal) comparison of techniques incomplete. Retrospective analyses [Secco 2002] or expert settings [Calvert 2000; Secco 2002] raise questions on reliability and generalisability. In one trial, a significant advantage was found favouring small-incision cholecystectomy with surgical residents performing 86% of the operations [Keus 2008c]. Overall, the trials showed a neutral or beneficial effect favouring the small-incision technique [McMahon 1994a; Barkun 1995; Calvert 2000; Srivastava 2001; Secco 2002; Nilsson 2004], and especially, the trials with low risk of bias favoured the small-incision technique [Calvert 2000; Nilsson 2004; Keus 2008c]. Qualitatively summarising cost results from the randomised trials we conclude that costs seem to be lower using small-incision cholecystectomy. Moreover, taking into account that our review did not find any significant differences between laparoscopic and small-incision cholecystectomy with respect to hospital stay and convalescence, it is even more likely that costs are lower using the small-incision approach.

Today with increasing budget restrictions we have to focus on the resource use associated with the available techniques. Savings, from an operation theatre perspective, have been reported as high as 23% when using the small-incision cholecystectomy technique. Reminding that cholecystectomy is one of the most frequently performed surgical procedures, saving resources by switching the technique of cholecystectomy offers opportunities for a re-allocation of these saved resources.

Symptom relief

Remarkably, very little to no information was available with respect to symptom relief. It seems logical that no recurrences of symptoms of gallbladder colic are to be expected when the gallbladder is removed. Especially when two different techniques for cholecystectomy are being compared, no differences in symptom relief are to be expected. However, data from lower level of evidence suggest that in up to 40% of patients, symptoms recur after cholecystectomy. Since this lower level of evidence is the best we have, the true figure remains unknown. Retrospectively, the diagnosis symptomatic cholecystolithiasis and the indication for cholecystectomy may not have been correct in these patients. Therefore, symptom relief should become the focus of research. Moreover, remembering the high complication proportions, it is very hard to justify the risks patients with incorrect diagnosis of symptomatic cholecystolithiasis and patients exposed to cholecystectomy with its unacceptable high complication rates are facing. Future research

urgently needs to refocus on outcomes critical for decision making, i.e., lowering the numbers of complications as well as achieving improvements in the accuracy of the diagnosis of symptomatic cholecystolithiasis.

Quality of the evidence

Trials with low risks of bias seem more likely to show no effect or a negative effect of laparoscopic surgery, whereas trials with high risk of bias seem more likely to show a positive effect or no effect of laparoscopic surgery. These observations are in accordance with other studies showing linkage between high risk of bias to significant overestimation of beneficial effects and underreporting of adverse effects. Trials with low risk of bias are more likely to estimate the 'true' effects of the interventions [Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Egger 2003; Wood 2008]. This overestimation of beneficial effects associated with laparoscopic surgery in trials with unclear or inadequate methodology may be an illustration of personal preferences of surgeons. Lack of objectivity biases results. Therefore, overall improvement of methodological quality of trials, and hence risk of bias, especially in surgery, is needed to obtain valid and reliable results.

We only based our assessment of bias on generation of the allocation sequence, allocation concealment, blinding, and follow-up. It is a weakness that we have not assessed bias due to selective outcome reporting, baseline differences, early stopping, and vested interests [Higgins 2008; Gluud 2009]. We plan to address these issues in future updates of the reviews.

Potential biases in the overview process

The first and most important potential source of bias relates to us, being the authors of all the three included Cochrane reviews. Additionally, we performed one of the trials with low risk of bias. We might not have recognised the potential mistakes conducted in the review process, neither may we be aware of any other potential sources of bias present in the three included reviews. In contrast, having critically appraised all individual trials, we are in detail informed on their weaknesses and strengths on which the reviews build. This may be an advantage.

A second issue are the risks of bias in the included trials. A systematic review summarises results of individual trials and collects their data into pooled effect estimates. The risks of bias are assessed to evaluate the validity of the intervention effects. Obviously, a review depends on the methodological quality of the individual trials and is never capable of increasing the strength of the trials with high risks of bias. In the third comparison, laparoscopic versus small-incision cholecystectomy, the overall risk of bias was considered relatively low, while in the other two comparisons the overall risk of bias in the

included trials was considered high. Therefore, the estimates of both minimal invasive techniques compared with the open technique may not be reliable estimates of the true intervention effects.

Agreements and disagreements with other studies or reviews

The total complication proportions we found in the laparoscopic versus the small-incision cholecystectomy comparison are 26.6% and 22.9%, respectively. These figures include gallbladder perforations. As some surgeons may not regard gallbladder perforation as a complication, our figures decrease to 17.0% and 17.5% if gallbladder perforation is excluded from our figures. However, these figures are still much higher than total complication figures up to 5% reported in other series and reviews including non-randomised series. Such studies represent lower levels of evidence [Southern Surgeons Club 1991; Litwin 1992; Deveney 1993; Deziel 1994; Downs 1996]. We are not aware of the exact reasons for the three times higher proportion of complications reported in randomised trials as compared to that originating from observational studies, but our findings are in accordance with previous observations [Papanikolaou 2006]. These observations point collectively to the fact that observational studies are more conservative than the randomised trial when reporting harm.

In the laparoscopic versus open cholecystectomy review, we found total complication proportions of 5.4% and 10.1%, respectively, with no significant difference applying the random-effects model. These figures differ from the laparoscopic versus small-incision cholecystectomy review (17.0% versus 17.5%). Probably differences in methodological quality of the trials may play a role. As results from high quality trials are more reliable [Schulz 1995;Wood 2008], we believe that the 17% is closer to the truth, particularly because the proportion of trials with low risk of bias in the laparoscopic versus small-incision cholecystectomy review outweighs the proportion of trials with low risk of bias in the laparoscopic versus open cholecystectomy review. The same arguments hold regarding the 17.5% complication proportion in small-incision cholecystectomy when compared to complication proportions in the small-incision versus open cholecystectomy review.

AUTHORS' CONCLUSIONS

Implications for practice

Both small-incision and laparoscopic cholecystectomy seem superior to open cholecystectomy. The question today is why the laparoscopic cholecystectomy has become the standard treatment of cholecystectomy for patients with symptomatic cholecystolithiasis without strong evidence showing it is superior to small-incision cholecystectomy.

We were unable to identify any outcome measure, significantly and convincingly in favour of the laparoscopic approach. There are no significant differences in mortality, complications, conversions, hospital stay, and convalescence on the low risk of bias evidence level. Other outcomes not suitable for pooling in meta-analyses, like pulmonary function, pain and analgesic use, and health status were not significantly different either. Operative time and costs were significantly different, both favouring the small-incision technique. From a patient-relevant outcomes perspective, both techniques may be considered equally effective. However, from a society perspective there seem to be advantages using the small-incision technique.

The high complication proportions observed in all three techniques in trials with low risk of bias raise questions and demand for ´best practice´ standardised technical guidelines for safer cholecystectomy procedures.

Implications for research

Research should concentrate on outcomes that are relevant to patients instead of focusing on outcomes that are of interest mainly to the surgeons. The causes of the high complication proportions need to be addressed. Furthermore, one additional trial with low risk of bias on a composite outcome measure 'serious adverse events' seems to be able to reach the cumulative information size needed for firm conclusions regarding the comparison small-incision versus laparoscopic cholecystectomy. Instead of considering total complications, which is a composite outcome measure, it may be more relevant to consider the individual complication categories since they may differ regarding their consequences to the patients. A number of the included trials did not report the specific subgroup of complications and their severity. Adverse event reporting is an issue that needs urgent attention in surgical trials. More elaborate cost evaluations, especially on a macro-economic level may provide additional arguments to decide on preferences for either one of both these techniques.

Reports on postoperative symptom relief are highly needed. The high failure rates of symptom relief suggested by lower level evidence raise questions on our quality of care. The lack of high quality evidence considering this patient relevant outcome is remarkable. We need a higher level of evidence to confirm or reject these failure rates. We urge trialists to conduct long-term follow-up to assess patient-relevant outcomes. If the figures originating from lower level of evidence appear to be true, then research should focus on improvements in the diagnostic process.

The high complication proportions in elective minimal invasive cholecystectomy should be our major concern. Today, research in surgery focuses on the widespread implementation of laparoscopy rather than improving critical patient relevant outcomes. We

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ought to worry about the patients' interests and take their perspective when considering a hierarchy of relevance of outcomes as recommended by the GRADE Working Group [Guyatt 2008a]. It is worrying that we focus on reducing hospital stay by implementing laparoscopic surgery rather than focusing on critical patient relevant outcomes. The overall quality of the included randomised trials varied with the majority of trials having several methodological deficiencies. The quality of trials needs to improve by adopting the CONSORT Statement (www.consort-statement.org).

There are several questions that still remain unanswered, like questions regarding pulmonary consequences after surgery, cost aspects, and more detailed questions on convalescence.

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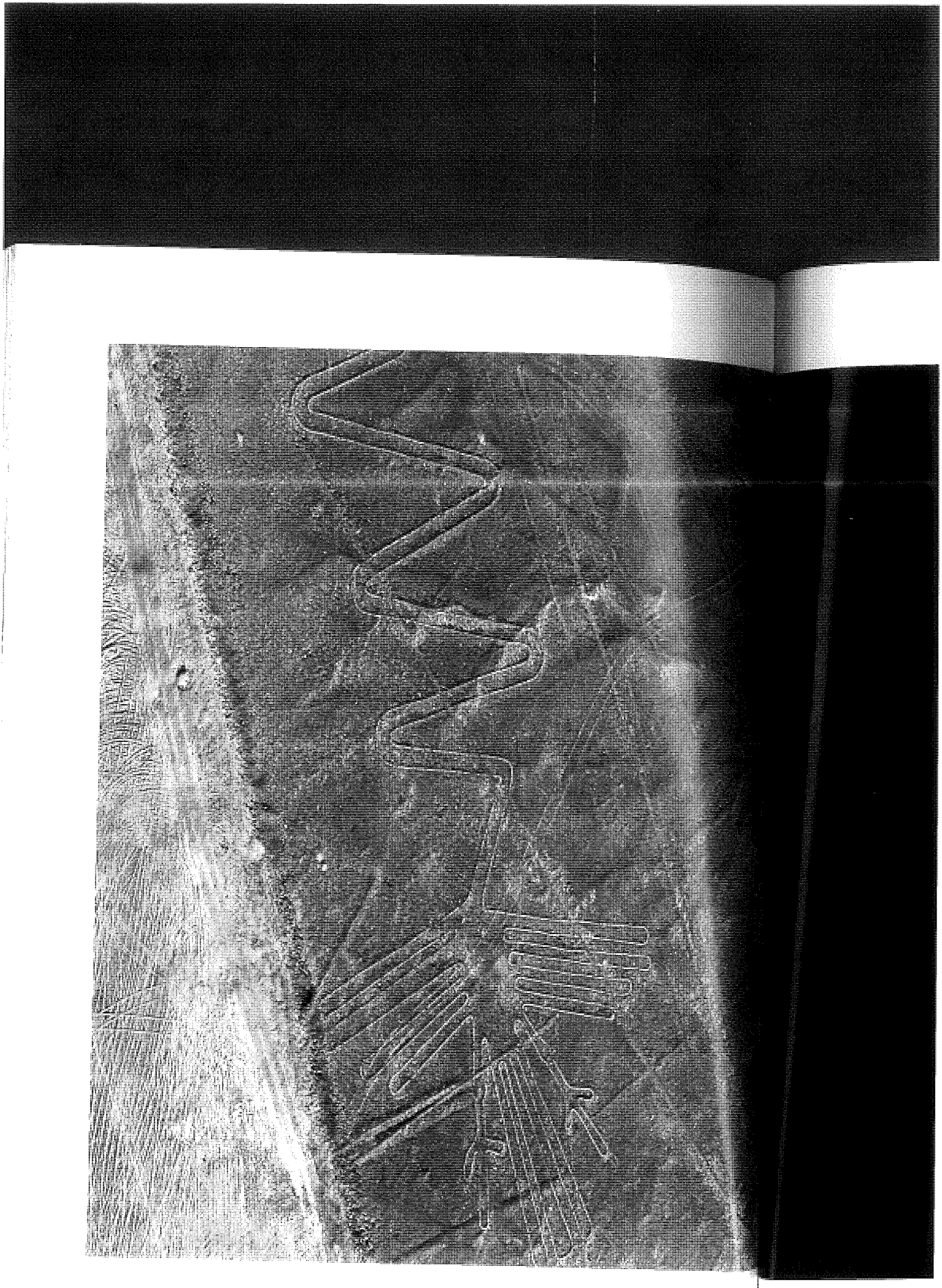

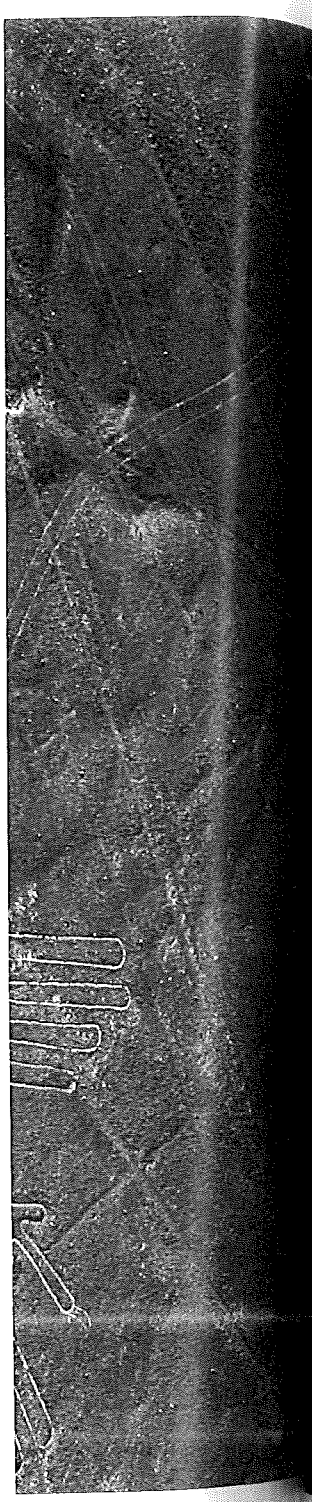

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Summary

Chapter 1 is the introduction of this thesis and presents a brief historical overview of cholecystectomy and the development of minimal invasive techniques.

Chapter 2 describes the method of evaluating clinical intervention research along the three most important dimensions in which a risk of error may be committed: systematic error (methodological quality), random error (the play of chance), and design errors (e.g. outcome measures). Using an example it is shown how available evidence may be analysed and eventually conclusions may be drawn from the evidence using a three-dimensional matrix approach.

The **chapters 3 until 12** present the results of this thesis.

Chapter 3 describes a systematic review comparing conventional open cholecystectomy with small-incision cholecystectomy. No significant differences were found considering complications between both techniques, but the small-incision technique has a shorter hospital stay.

Chapter 4 describes a systematic review comparing conventional open cholecystectomy with laparoscopic cholecystectomy. No significant differences were found considering complications and operative time between both techniques, but the laparoscopic technique has a quicker convalescence.

Chapter 5 describes a systematic review comparing laparoscopic cholecystectomy with small-incision cholecystectomy. No significant differences were found considering complications and convalescence between both techniques, but the small-incision technique has a shorter operative time.

Chapters 3, 4, and 5 show that both minimal invasive techniques (laparoscopic and small-incision cholecystectomy) have a quicker recovery compared with conventional open cholecystectomy, which justifies that both minimal invasive techniques are preferred over the conventional open cholecystectomy. Based on these findings both minimal invasive techniques should be further evaluated and balanced.

Chapter 6 evaluates whether the conclusions in chapter 5 are influenced by the chosen statistical pooling method. Multiple choices have to be made in meta-analysis considering the statistical pooling method, especially when no events occur in one or both groups of a trial (zero-event trials). The analyses show that choices of the statistical pooling method may very well influence the conclusions drawn from meta-analysis. Multiple analyses are therefore needed to evaluate the robustness of conclusions. Detailed analyses of both minimal invasive techniques for cholecystectomy show that

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there are no significant differences considering complications between laparoscopic and small-incision cholecystectomy.

In **chapter 7** a new statistical technique for meta-analyses, called trial sequential analysis, is used for the assessment of the risk of random error. This technique evaluates whether definitive evidence has been reached or whether significant findings may be caused by spurious findings. This technique may also estimate how many additional randomized patients are needed before firm evidence may be reached to accept or reject potential differences between two interventions. The results show that there are no significant differences between laparoscopic and small-incision cholecystectomy. Moreover, it is highly unlikely that a difference in complications between laparoscopic and small-incision cholecystectomy will ever be shown in the future.

The results in **chapter 5, 6 and 7** show that there are no significant differences in primary outcome measures (mortality and complications) between laparoscopic and small-incision cholecystectomy, accounting for risks of systematic and random error. Therefore, it seems justified to prefer laparoscopic or small-incision cholecystectomy based on secondary outcome measures (chapters 8 until 11).

Chapter 8 shows the results of a randomized trial between laparoscopic and small-incision cholecystectomy in a Dutch general teaching hospital focusing on a difference in costs. The numbers of complications in the trial are in line with the results in chapter 5. The large majority of the operations were performed by surgical residents. The numbers of procedures converted to conventional open cholecystectomy, hospital stay, and return back to work were also not significantly different between both minimal invasive techniques. Operative time was significantly shorter using the small-incision approach.

Chapter 9 shows the results of pulmonary function and blood gas analyses of the patients in the trial. Anaesthesia techniques, analgesic use, and peri-operative care in the trial were standardized by protocol. No significant differences were found in pulmonary function and blood gas analyses between laparoscopic and small-incision cholecystectomy.

Chapter 10 describes the results of health status and cosmesis evaluated by questionnaires of all patients in the trial. The SF-36 and Gastrointestinal Quality of Life Index (GIQLI) were used to evaluate health status and the Body Image Questionnaire was used to evaluate cosmesis. No significant differences considering health status and cosmesis were found between the laparoscopic and the small-incision technique.

Chapter 11 shows the results of the cost analysis of the trial comparing laparoscopic and small-incision cholecystectomy. A cost-minimisation analysis was conducted from

a societal perspective including direct and indirect costs. The results of the cost analysis show that the small-incision technique is preferred, both from a hospital and from a societal perspective. From a societal perspective the costs caused by work-leave appear to contribute the largest part of all costs irrespective the operative technique used.

In **chapter 12** the results of a qualitative research study are described. The aim was to identify all aspects and factors that influence the moment of return to work by using focus groups and to compare responses from patients and physicians. It appears that physicians perceive their advices as an important factor in patients' duration of sick-leave. In contrast, patients seldom mention this factor and experience physical complaints as the major reason influencing the moment of return to work.

Chapter 13 is the discussion of this thesis. The available evidence considering cholecystectomy for symptomatic cholecystolithiasis is summarized in an overview review of Cochrane Hepato-Biliary Group reviews along the perspective of the three most important dimensions of the risks of error: systematic error (methodological quality), random error (the play of chance), and design error (e.g. outcome measures). Laparoscopic and small-incision cholecystectomy are both preferred over conventional open cholecystectomy based on a quicker recovery. No significant differences are found between laparoscopic and small-incision cholecystectomy considering complications and analysis of the risk of random error using trial sequential analysis shows that it is highly unlikely that a difference in complications will ever be found in the future. There are also no significant differences in numbers of conversions, hospital stay, convalescence, pulmonary function, analgesic use, health status, and cosmesis between laparoscopic and small-incision cholecystectomy. The small-incision technique has a shorter operative time and is associated with lower costs, both from a hospital and a societal perspective. Both techniques appear applicable in a teaching hospital. Both minimal-invasive techniques may be considered equally effective from a patient perspective, however, the small-incision technique is preferred from a societal perspective based on a quicker operative time and lower costs.

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Samenvatting

Hoofdstuk 1 vormt de inleiding van dit proefschrift en geeft een kort historisch overzicht van de cholecystectomie en de ontwikkeling van minimaal-invasieve technieken.

Hoofdstuk 2 beschrijft de methode van interventie onderzoek waarin de drie belangrijkste dimensies van mogelijke fouten in onderzoek worden beschreven: systematische fouten (methodologische kwaliteit), toevallige fouten en uitkomstmaten. Aan de hand van een voorbeeld wordt getoond hoe bestaand onderzoek met elkaar vergeleken kan worden en uiteindelijk een conclusie getrokken kan worden uit het aanwezige bewijs met behulp van een drie-dimensionele matrix benadering.

De **hoofdstukken 3 t/m 12** tonen de resultaten van dit proefschrift.

Hoofdstuk 3 beschrijft een systematische review waarin de conventionele open cholecystectomie wordt vergeleken met de 'small-incision' cholecystectomie. Er worden geen verschillen in complicaties gevonden, maar de 'small-incision' techniek kent een kortere opnameduur.

Hoofdstuk 4 beschrijft een systematische review waarin de laparoscopische cholecystectomie wordt vergeleken met de conventionele open cholecystectomie. Er worden geen verschillen in complicaties en in operatieduur gevonden, maar de laparoscopische techniek kent een sneller herstel.

Hoofdstuk 5 beschrijft een systematische review waarin de laparoscopische cholecystectomie wordt vergeleken met de 'small-incision' cholecystectomie. Er worden geen verschillen in complicaties gevonden en ook niet in duur van herstel, maar de 'small-incision' techniek kent een kortere operatieduur.

In de **hoofdstukken 3, 4 en 5** wordt gevonden dat beide minimaal-invasieve technieken (laparoscopische en 'small-incision' cholecystectomie) een sneller herstel kennen dan de conventionele open cholecystectomie, waardoor het gerechtvaardigd is beide minimaal-invasieve technieken de voorkeur te geven boven de conventionele open cholecystectomie. Op basis van deze bevindingen moeten beide minimaal-invasieve technieken verder geevalueerd en tegen elkaar afgewogen worden.

In **hoofdstuk 6** wordt nagegaan in hoeverre de conclusies in hoofdstuk 5 worden beïnvloed door de gekozen statistiche analyse methode. Bij het verrichten van een meta-analyse moeten er verschillende keuzes worden gemaakt wat betreft de te gebruiken statistische technieken, met name als er onderzoeken zijn waarin geen gebeurtenissen voorkomen in een of beide groepen ('zero-event trials'). Het blijkt dat de gekozen statis-

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tische analyse techniek voor het 'poolen' van de data de conclusie kan beinvloeden. Hierdoor lijkt het verstandig om meerdere analyses te verrichten om de robuustheid van de conclusies te ondersteunen. Bij gedetailleerde analyse van beide minimaal-invasieve technieken voor cholecystectomie blijken er geen verschillen te bestaan wat betreft complicaties tussen beide technieken.

In **hoofdstuk 7** wordt met behulp van een nieuwe statistische analyse techniek voor meta-analyses 'trial sequential analysis', geevalueerd of er sprake is van toevallige fouten. Deze techniek analyseert of er voldoende zekerheid is of een verschil tussen beide minimaal-invasieve technieken aanwezig is of hoeveel patienten nog nodig zijn om een zeker verschil tussen beide technieken aan te kunnen tonen. Er blijken geen verschillen in complicaties te bestaan tussen laparoscopische en 'small-incision' cholecystectomie en het is hoogst onwaarschijnlijk dat er ooit nog een verschil in complicaties tussen beide technieken aangetoond gaat worden.

Op basis van de resultaten in de **hoofdstukken 5, 6 en 7** blijken er geen verschillen in primaire uitkomstmaten (mortaliteit en complicaties) te bestaan tussen laparoscopische en 'small-incision' cholecystectomie, rekening houdend met mogelijke fouten in methodologische kwaliteit en toevallige fouten. Derhalve lijkt het gerechtvaardigd om op basis van secundaire uitkomstmaten een keuze te maken voor een van beide technieken (hoofdstukken 8 tot en met 11).

In **hoofdstuk 8** worden de resultaten beschreven van een gerandomiseerde trial gericht op een verschil in kosten tussen laparoscopische en 'small-incision' cholecystectomie in een Nederlands opleidingsziekenhuis. De aantallen complicaties komen overeen met de gevonden resultaten in hoofdstuk 5. Het overgrote deel van de operaties werden door chirurgen in opleiding uitgevoerd. Aantallen conversies naar conventionele open cholecystectomie, opnameduur en duur van herstel zijn eveneens niet significant verschillend. De operatieduur was significant korter voor de 'small-incision' techniek.

In **hoofdstuk 9** worden de resultaten beschreven van de longfunctie onderzoeken en bloedgas analyses van de patienten in de trial. Anaesthesie technieken, analgetica en perioperatieve zorg waren in de trial gestandaardiseerd voor alle patienten. Er werden geen verschillen gevonden in longfunctie onderzoek en bloedgas analyses tussen laparoscopische en 'small-incision' cholecystectomie.

In **hoofdstuk 10** worden de resultaten beschreven van de vragenlijsten die voorgelegd zijn aan alle patienten in de trial om de gezondheidstoestand ('health status') en de cosmetiek te evalueren. Hiertoe werden de SF-36 en de GIQLI vragenlijsten gebruikt

voor de gezondheidstoestand en de Body Image Questionnaire voor de cosmetiek. Er werden geen verschillen in gezondheidstoestand en cosmetiek gevonden tussen de laparoscopische en 'small-incision' techniek.

In **hoofdstuk 11** worden de resultaten beschreven van de kosten analyse van de trial waarin de laparoscopische en 'small-incision' cholecystectomie worden vergeleken. Er werd een kosten-minimalisatie analyse verricht vanuit een maatschappij perspectief waarin alle directe medische kosten en indirecte niet-medische kosten werden meegenomen. Zowel vanuit een ziekenhuis perspectief als vanuit een maatschappij perspectief heeft de 'small-incision' techniek de voorkeur. Ongeacht de operatietechniek zijn vanuit een maatschappij perspectief de kosten als gevolg van ziekteverlof de belangrijkste kostenpost.

In **hoofdstuk 12** worden de resultaten van een kwalitatief onderzoek beschreven. Met behulp van focus groepen werden discussies gevoerd met zowel patienten als artsen om een inzicht te verkrijgen in de redenen waarom patient juist snel het werk hervatten en waarom werkhervatting soms lang duurt. Het blijkt dat artsen verwachten dat hun advies de belangrijkste factor is in de duur van het ziekteverlof terwijl patienten aangeven dat lichamelijke klachten de belangrijkste redenen zijn.

Hoofdstuk 13 vormt de discussie van dit proefschrift. In een 'overview review' wordt het beschikbare bewijs beschreven voor cholecystectomie vanwege symptomatische cholecystolithiasis in het perspectief van methodologische kwaliteit, toevallige fouten en uitkomstmaten. Op basis van een sneller herstel hebben laparoscopische en 'small-incision' cholecystectomie de voorkeur boven conventionele open cholecystectomie. Er zijn geen verschillen in complicaties gevonden tussen laparoscopische en 'small-incision' cholecystectomie en analyse van de kans op toevallige fouten toont dat het hoogst onwaarschijnlijk is dat er ooit nog een verschil in deze uitkomstmaat tussen beide technieken aangetoond zal worden. Er zijn ook geen verschillen in aantallen conversies, opnameduur, duur van herstel, longfunctie, analgetica gebruik, gezondheidstoestand en cosmetiek tussen laparoscopische en 'small-incision' cholecystectomie. De 'small-incision' techniek heeft een kortere operatieduur en kent lagere kosten, zowel vanuit een ziekenhuis als een maatschappij perspectief. Beide technieken blijken goed toepasbaar in een opleidingssituatie. Vanuit een patienten perspectief kunnen beide minimaal-invasieve technieken gelijkwaardig worden beschouwd, maar vanuit een maatschappij perspectief heeft de 'small-incision' techniek de voorkeur op basis van een kortere operatieduur en lagere kosten.

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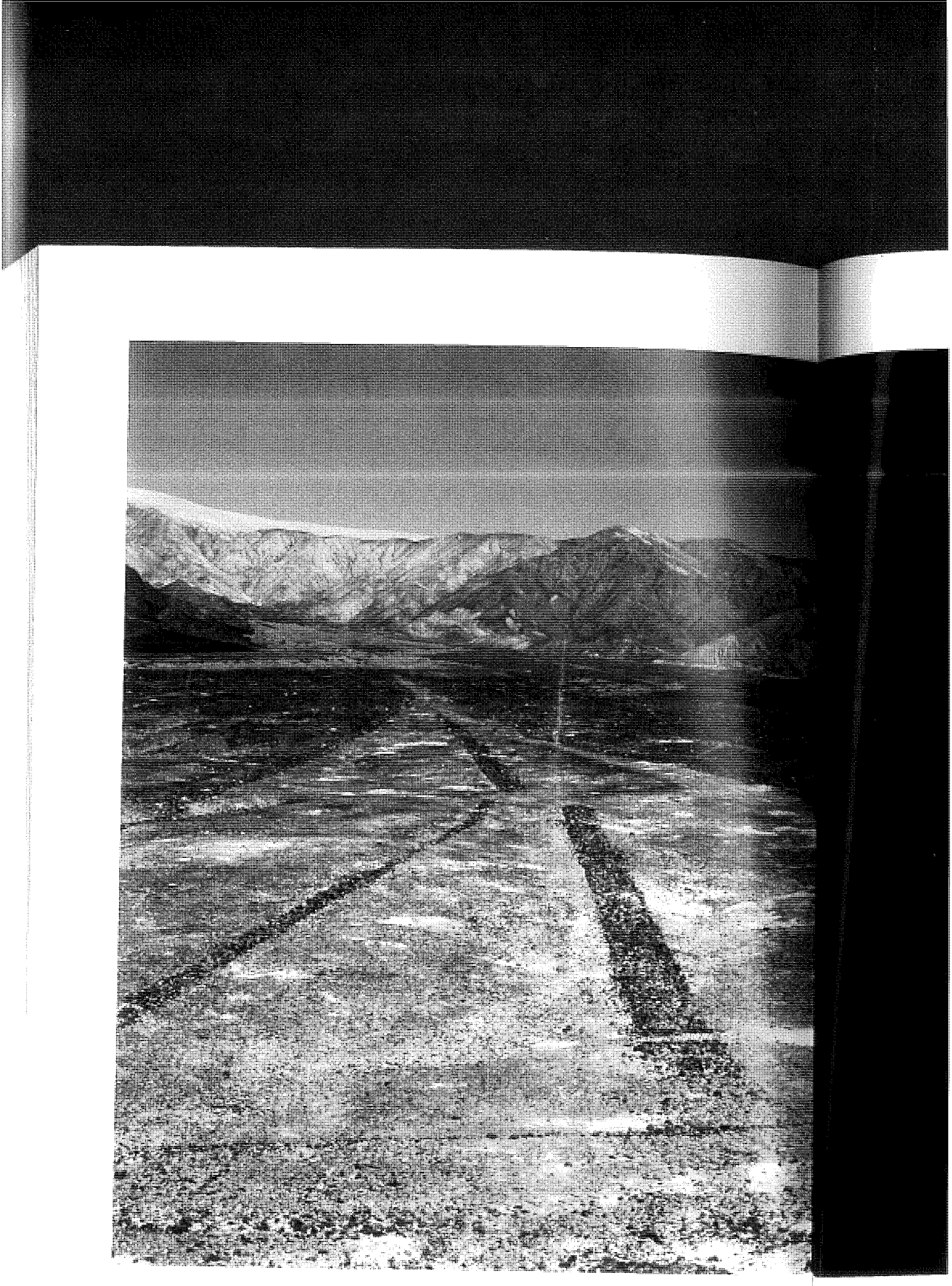

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Promoveren doe je niet alleen. Velen hebben op welke manier dan ook een bijdrage geleverd aan het tot stand komen van dit proefschrift. Zonder hun hulp was dit proefschrift onmogelijk geweest. Ik wil iedereen bedanken, maar enkelen wil ik graag in het bijzonder noemen.

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The Copenhagen Trial Unit and The Cochrane Hepato-Biliary Group, Copenhagen, Denmark: Dima, Sarah, Kate, and all others, thanks for all your excellent support.

Verder wil ik
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Verder wil ik graag alle onderstaande personen hartelijk danken voor hun bijdrage, zonder de illusie te hebben compleet te zijn:

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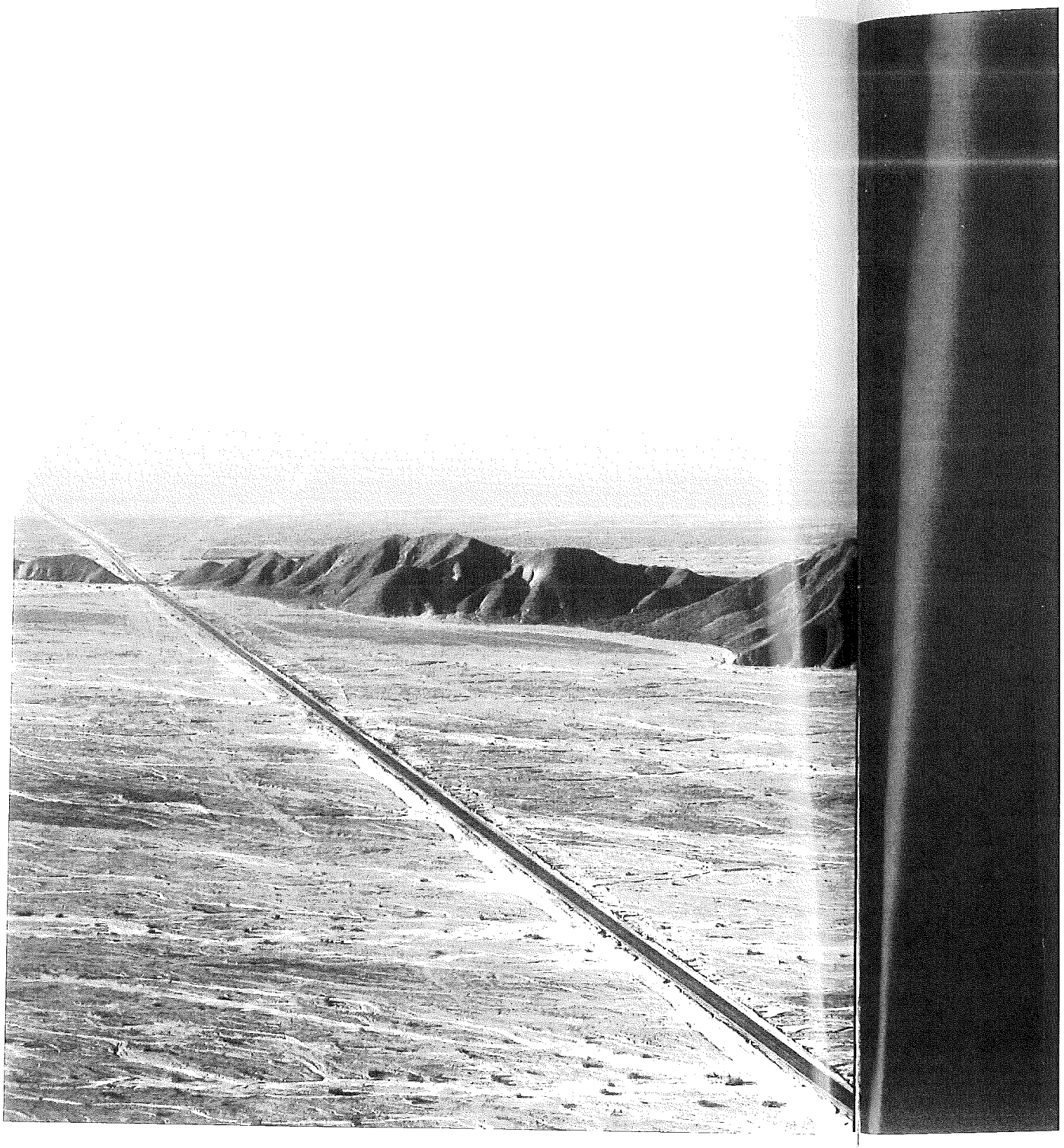
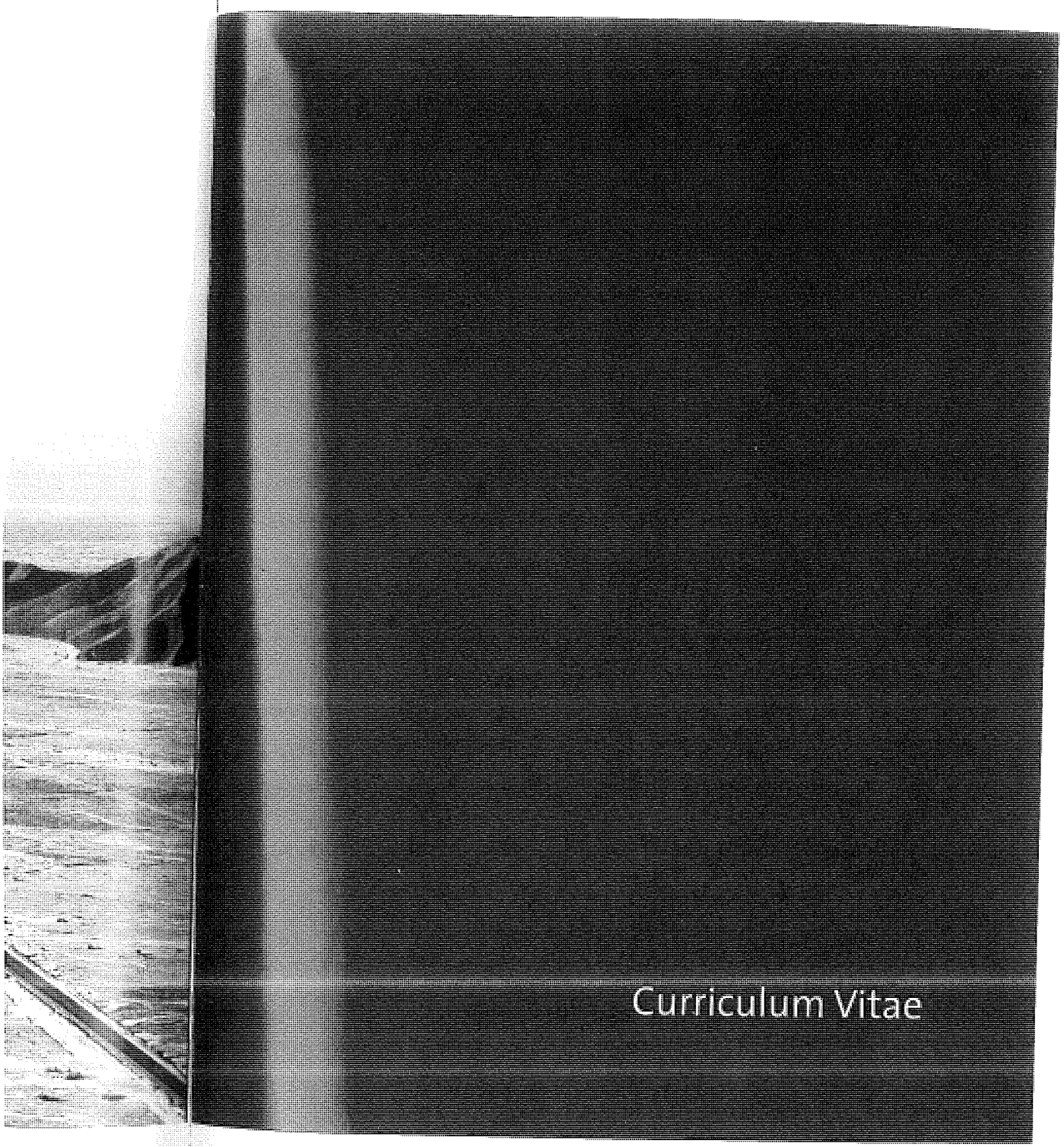
Alle huisartsen en arbo artsen die hebben deelgenomen aan de focus groep discussies.

Alle patienten die hebben deelgenomen aan de trial.





Curriculum Vitae

CURRICULUM VITAE

Frederik (Eric) Keus werd geboren op 15 oktober 1972 in Almelo. Na het behalen van zijn eindexamen VWO aan het Christelijk Lyceum in Almelo studeerde hij geneeskunde aan de Universiteit van Antwerpen. In juni 1999 werd het artsexamen behaald en aansluitend begon hij te werken als arts assistent (ANIOS) in het Diakonessenhuis in Utrecht. Van januari 2000 to december 2002 werkte hij als arts assistent (ANIOS) in het St. Elisabeth ziekenhuis in Tilburg. Het onderzoek hetgeen uiteindelijk heeft geleid tot dit proefschrift werd gestart in het St. Elisabeth ziekenhuis in Tilburg in januari 2000. In Januari 2003 begon hij de opleiding tot chirurg in het Universitair Medisch Centrum te Utrecht (opleider prof. dr. I. H. M. Borel Rinkes), welke vanaf januari 2005 werd voortgezet in het Diakonessenhuis te Utrecht (opleider dr. G. J. Clevers). Hij was lid van de comissie richtlijnen diagnostiek en behandeling van galsteenlijden (2005). In 2007 en 2008 volgde hij het theoretische deel van de master opleiding Clinical Epidemiology aan de Universiteit Utrecht. Sinds 2008 is hij editor van de Cochrane Hepato-Biliary Review Group.
Sinds 1 april 2009 is hij chirurg en momenteel werkzaam als fellow onco/GE op de afdeling Heelkunde in het Universitair Medisch Centrum St. Radboud in Nijmegen (afdelingshoofd prof. dr. C. J. H. M. van Laarhoven, MSc.).