Meta-analysis

Meta-analysis of endoscopy and surgery *versus* surgery alone for common bile duct stones with the gallbladder *in situ*

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Background: **There is no clear consensus on the better therapeutic approach (endoscopic *versus* surgical) to choledocholithiasis. This study is a meta-analysis of the available evidence.**

Methods: **A search of the Medline and ISI databases identified 12 studies that met the inclusion criteria for data extraction. The analysis was performed using a random-effects model. The outcome was calculated as an odds ratio (OR) or relative risk (RR) with 95 per cent confidence intervals (c.i.).**

Results: **Outcomes of 1357 patients were studied. There was no significant difference in successful duct clearance (OR 0·85 (95 per cent c.i. 0·64 to 1·12); $P = 0·250$), mortality (RR 1·79 (95 per cent c.i. 0·66 to 4·83); $P = 0·250$), total morbidity (RR 0·89 (95 per cent 0·71 c.i. to 1·13); $P = 0·350$), major morbidity (RR 1·34 (95 per cent c.i. 0·92 to 1·97); $P = 0·130$) or need for additional procedures (OR 1·37 (95 per cent c.i. 0·82 to 2·29); $P = 0·230$) between the endoscopic and surgical groups. There was also no significant difference between the endoscopic and laparoscopic surgery groups.**

Conclusion: **Both approaches have similar outcomes, and treatment should be determined by local resources and expertise.**

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Introduction

Common bile duct (CBD) calculi are present in 4–10 per cent of those presenting with indications for cholecystectomy[1–4] and their management is controversial[5–7]. In the era of open cholecystectomy, the routine use of intraoperative cholangiography meant that detection of choledocholithiasis resulted in exploration of the CBD and a one-stage approach to complicated biliary disease[8,9]. With the introduction of laparoscopic cholecystectomy, there was a move away from intraoperative cholangiography and surgical management of CBD stones towards a two-stage procedure with the use of preoperative or postoperative endoscopic retrograde cholangiopancreatography (ERCP)[10]. This was mainly due to the lack of surgical expertise in laparoscopic common duct exploration and reluctance to convert to open surgery. Complex algorithms were developed[11,12] aimed at predicting the presence of occult choledocholithiasis to select those most likely to benefit from preoperative ERCP, yet a significant false-positive rate remained[13]. A combined approach of laparoscopic intraoperative cholangiography with selective postoperative ERCP to avoid unnecessary procedures has since been proposed[14]. However, ERCP is associated with significant morbidity and mortality[15]. With the development of accurate preoperative non-invasive CBD imaging based on magnetic resonance cholangiopancreatography, further complex preoperative algorithms were instituted[16]. Today, the laparoscopic management of choledocholithiasis is increasingly reported with the emergence of an argument to return to one-stage surgical management of choledocholithiasis[17]; this has not been widely accepted by general surgeons[5].

There is now equipoise as to whether surgical treatment alone (open or laparoscopic) or a combined endoscopic–surgical approach is the more effective treatment strategy for the management of choledocholithiasis in association with cholecystolithiasis. Furthermore, if endoscopic treatment is used in conjunction with surgery, is it better to operate before or after endoscopy? Several randomized controlled trials have been published in an

attempt to answer one or other, or both, of the above questions. What follows is a meta-analysis of these studies.

Methods

This meta-analysis was conducted according to recommendations of the QUORUM statement[18] (*Fig. 1*).

Inclusion and exclusion criteria

Only randomized controlled trials published as original articles in the English language up to the end of March 2006 were considered. Review articles, retrospective analyses and abstracts were not included.

Identification of studies

All randomized controlled trials citing endoscopic *versus* surgical management of CBD stones were identified by conducting an electronic search of the Medline and ISI databases using the following keywords: bile duct stones/calculi, ERCP, endoscopic sphincterotomy, laparoscopic ductal clearance/choledochotomy/exploration. A comprehensive hand-based search of reference lists of published articles and review articles was performed to ensure inclusion of all possible studies and exclude duplicates (two trials were excluded for this reason[19,20]).

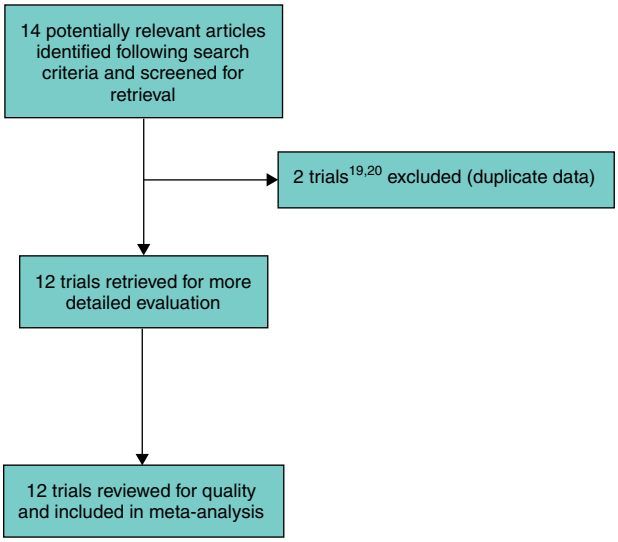

Fig. 1 Search strategy for randomized controlled trials comparing the outcome of surgery and endoscopic management of choledocholithiasis in those patients with the gallbladder *in situ*

Data extraction

All included trials were reviewed independently by two authors and data extracted according to a predefined review form (*Fig. 2*). Total complications were recorded as the total number of patients experiencing at least one complication, and so it is possible for the sum of individual complications to be greater than the total number of patients experiencing one complication within any given study. Conversion to open surgery in the laparoscopic CBD exploration cohort was counted as morbidity. Major complications were defined as intra-abdominal sepsis, cholangitis, clinical pancreatitis, pneumonia, major

Trial design	Author	
	Country	
	RCT	Yes/No
	Multicentre	Yes/No
	Study period	Months
	Randomization documented	Yes/No
	Total no. in study	
	Surgeon selection standardized	
	Cost	Yes/No
	Blinded	
	Study groups	Yes/No
	n	
	CONSORT score	
Exclusion criteria	Cholangitis	Yes/No
	Pancreatitis	Yes/No
	Duct size at IOC	Yes/No
	Preoperative ERCP	Yes/No
Patient factors	Mean age	
	Median age	
	Sex	Male/Female
	Gallbladder *in situ*	Yes/No
	Clinical history	Jaundice
		Cholangitis
		Pancreatitis
Outcome	Operating time (mean)	Minutes
	Morbidity	
	Mortality	
	Retained stone rate	
	Duct clearance	
	Reoperation rate	
	Repeat ERCP rate	
	Hospital stay (median)	
	Conversion rate	Days
	Length of follow-up (median)	
		Months
Complications		
Local		
	Pancreatitis	
	Bile leak	
	Gastrointestinal bleed	
	Bleeding/wound infection	
	Sepsis	
Systemic	Cardiovascular pulmonary renal insufficiency	
Conclusion		

RCT, randomized controlled trial; *n*, number of patients per study group; IOC, intraoperative cholangiography; ERCP, endoscopic retrograde cholangiopancreatography.

Fig. 2 Data extraction proforma

bleeding (requiring transfusion or intervention), myocardial infarction, stroke and early unplanned reoperation. Minor complications were biochemical pancreatitis, minor bile leak, atelectasis, wound infection and urinary tract infection. Additional procedures were defined as any endoscopic or surgical procedure for failed duct clearance or for management of complications.

Each trial was assessed for quality using the CONSORT checklist for reporting randomized trials[18]. A point was given for each criterion that was met (maximum score 22). Differences in assessment were discussed among all authors until agreement was achieved. Data were analysed on an intention-to-treat basis.

Statistical analysis

The analysis was performed using Review Manager 4·2·7 (The Cochrane Collaboration, Oxford, UK). All analyses were performed on dichotomous outcomes. The outcome was calculated with a random-effects model as an odds ratio (OR) or relative risk (RR) with 95 per cent confidence intervals (c.i.) using the Mantel–Haenszel method. The level of significance was set at $P < 0{\cdot}050$. Heterogeneity was evaluated using the Q statistic.

Results

The search strategy identified 12 randomized trials that met the inclusion criteria (*Table 1*). Seven compared endoscopy and surgery against open CBD surgery[21–27] and five compared endoscopy and surgery against laparoscopic CBD surgery[28–32] (including one study that compared intraoperative endoscopy against laparoscopic CBD surgery[32]). Outcomes for 1357 patients (652 in the endoscopy plus surgery group, 705 in the CBD surgery group) were examined. A separate analysis comparing the endoscopy plus surgery (353 patients) and laparoscopic CBD surgery alone (391 patients) was also performed.

Forest plots (*Figs 3–7*) were constructed comparing successful duct clearance, mortality, total morbidity, major morbidity and need for additional procedures for endoscopy plus surgery against CBD surgery. Heterogeneity between studies was not significant (data shown in figures).

Table 1 Summary of randomized trials comparing endoscopic common duct clearance plus surgery against surgery alone

Reference (year)	Treatment	*n*	Successful duct clearance	Mortality	Morbidity (Total)	Morbidity (Major)	Additional procedures required	Median hospital stay (days)
21 (1987)	ES	55	50	2	18	9	1	9
	S	59	54	1	13	5	0	11
22 (1991)	ES	26	17	0	4	1	n.a.	5
	S	26	23	0	7	1	n.a.	6
23 (1992)	ES	16	5	0	3	0	1	n.a.
	S	18	6	0	3	0	0	n.a.
24 (1995)	ES	39	35	0	7	3	4	n.a.
	S	41	37	0	9	4	4	n.a.
25 (1996)	ES	50	44	3	8	5	n.a.	5
	S	48	45	2	11	4	n.a.	11
26 (1996)	ES	16	11	0	5	4	2	10·6
	S	17	13	0	5	3	3	11·3
27 (1998)	ES	97	67	3	13	13	28	12
	S	105	75	1	13	5	8	16
28 (1998)	ES	40	37	0	6	4	10	3·5
	S	40	30	0	7	2	10	1
29 (1999)	ES	133	82	2	17	9	17	9
	S	133	92	1	21	9	17	6
30 (2005)	ES	45	43	0	11	6	3	7·7
	S	41	40	0	12	7	3	6·4
31 (2002)	ES	42	27	1	6	3	5	9
	S	36	24	1	5	2	4	7·4
32 (2006)	ES	93	85	0	8	1	1	4·2
	S	141	126	0	22	1	3	4·6
Total	ES	652	503(77·1)	11 (1·69)	106 (16·25)	58 (8·89)	72 (12·5)	
	S	705	565(80·1)	6 (0·85)	128 (18·15)	43 (6·1)	52 (8·2)	

Values in parentheses are percentages. ES, endoscopy plus surgery; S, surgery alone; n.a., data not available

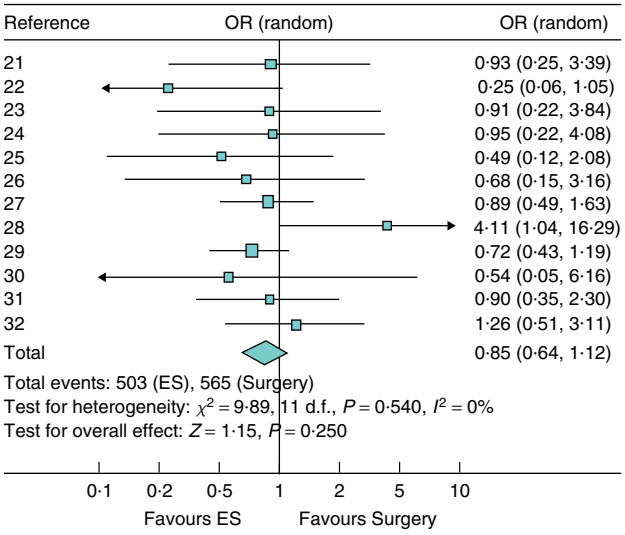

Fig. 3 Successful duct clearance: endoscopy plus surgery (ES) *versus* surgery alone. Odds ratios (ORs) are shown with 95 per cent confidence intervals

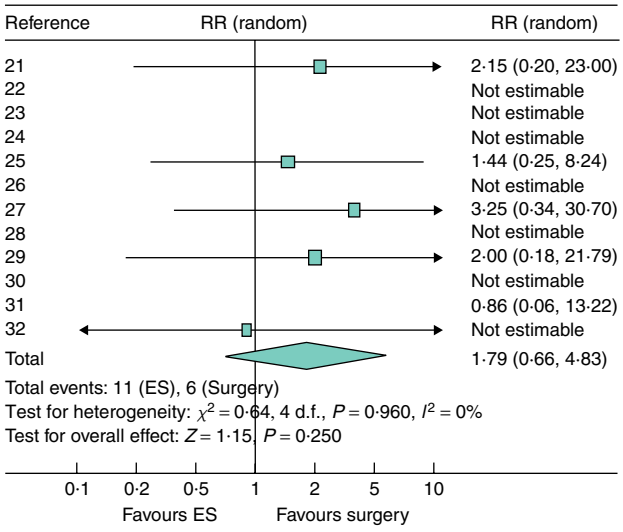

Fig. 4 Mortality after common bile duct clearance: endoscopy plus surgery (ES) *versus* surgery alone. Relative risk (RR) values are shown with 95 per cent confidence intervals

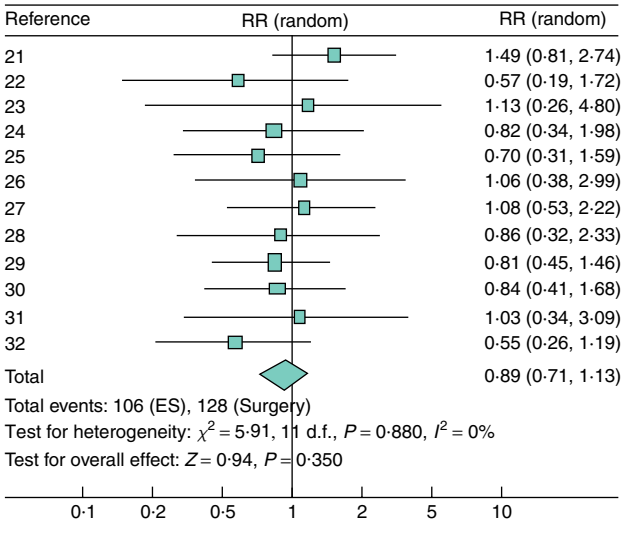

Fig. 5 Total morbidity after common bile duct clearance: endoscopy plus surgery (ES) *versus* surgery alone. Relative risk (RR) values are shown with 95 per cent confidence intervals

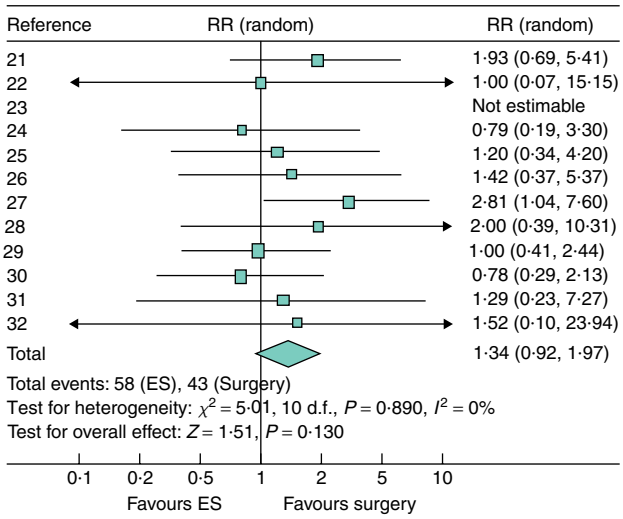

Fig. 6 Major morbidity after common bile duct clearance: endoscopy plus surgery (ES) *versus* surgery alone. Relative risk (RR) values are shown with 95 per cent confidence intervals

Successful duct clearance was achieved in 77·1 per cent of patients in the endoscopy plus surgery group and in 80·1 per cent in the CBD surgery group (OR 0·85 (95 per cent c.i. 0·64 to 1·12); $P = 0·250$) (*Fig. 2*). Successful duct clearance was achieved in 77·6 per cent of the endoscopy plus surgery group and in 79·8 per cent in the laparoscopic CBD surgery group (OR 1·05 (95 per cent c.i. 0·61 to 1·8); $P = 0·870$).

The mortality rate was 1·7 per cent in the endoscopy plus surgery group and 0·9 per cent in the CBD surgery group (RR 1·79 (95 per cent c.i. 0·66 to 4·83); $P = 0·250$) (*Fig. 4*). There was no significant difference in mortality rate between the endoscopy plus surgery group (0·9 per cent) and the laparoscopic CBD surgery group (0·5 per cent) (RR 1·39 (95 per cent c.i. 0·23 to 8·38); $P = 0·720$).

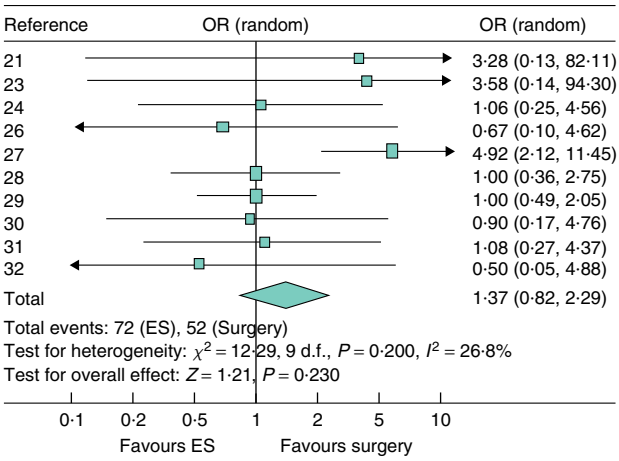

Fig. 7 Additional procedures after initial intervention: endoscopy plus surgery (ES) *versus* surgery alone. Odds ratios (ORs) are shown with 95 per cent confidence intervals

The total morbidity rate was 16·3 per cent in the endoscopy plus surgery group and 18·2 per cent in the CBD surgery group (RR 0·89 (95 per cent 0·71 to 1·13); $P = 0{\cdot}350$) (*Fig. 5*). The total morbidity rate was 13·6 per cent in the endoscopy plus surgery group and 17·1 per cent in the laparoscopic CBD surgery group (RR 0·93 (95 per cent c.i. 0·65 to 1·34); $P = 0{\cdot}710$).

The major morbidity rate was 8·9 per cent in the endoscopy plus surgery group and 6·1 per cent in the CBD surgery group (RR 1·34 (95 per cent c.i. 0·92 to 1·97); $P = 0{\cdot}130$) (*Fig. 6*). There were no differences in major morbidity between the endoscopy plus surgery group (6·5 per cent) and the laparoscopic CBD surgery group (5·4 per cent) (RR 1·05 (95 per cent c.i. 0·59 to 1·86); $P = 0{\cdot}870$).

There was a need for additional procedures after the initial intervention in 12·5 per cent of patients in the endoscopy plus surgery group and 8·2 per cent in the CBD surgery group (OR 1·37 (95 per cent c.i. 0·82 to 2·29); $P = 0{\cdot}230$) (*Fig. 7*). There was also no significant difference with regard to additional procedures between the endoscopy plus surgery group (10·2 per cent) and the laparoscopic CBD surgery group (9·5 per cent) (OR 0·97 (95 per cent c.i. 0·59 to 1·60); $P = 0{\cdot}900$).

Discussion

This study depends on 12 randomized trials comparing two approaches. Despite cholecystectomy being a common operation and with choledocholithiasis complicating up to 10 per cent of cases of symptomatic cholelithiasis[3], all the trials were relatively small; only four[21,27,29,32] randomized more than 50 patients to each arm. A significant risk of a Type 2 error exists with each individual trial. Previous power estimations indicated that at least 158 patients would be required to detect a 20 per cent difference in overall morbidity between the two groups ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}2$)[21] and 86 to detect a 25 per cent difference ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}2$)[30].

The results of the present analysis confirm that ERCP or surgical common duct exploration are equivalent treatments in terms of duct clearance, mortality and overall morbidity. In particular, they do not support the widely held belief that failed postoperative ERCP increases patient morbidity. A subgroup analysis of those patients undergoing laparoscopic duct exploration compared with endoscopic clearance also failed to show any significant difference.

The included trials were analysed on an intention-to-treat basis as this reduces bias and tends to answer a question of clinical relevance. However, it is important to consider the inclusion criteria for each of the studies when applying the results to clinical practice. Two trials excluded patients from laparoscopic CBD exploration if the duct was less than 6 mm in diameter[28,30], although the authors performed transcystic exploration where feasible.

It is important also to note that, although the laparoscopic technique appears to be equivalent to ERCP and may be more cost effective[17,33], it has not been widely accepted by the surgical community[17]. A recent survey of general surgeons practising in the USA showed that, although 30 (44 per cent) of 68 confirmed they could perform laparoscopic CBD exploration, only 15 (22 per cent) actually did so routinely[5]. The most common reasons for not doing so were that the procedure was too time consuming and lack of equipment.

Given the results of the present study it seems reasonable to adapt the approach to choledocholithiasis according to local expertise and conditions. In those institutions where access to ERCP is difficult the preferred approach should be surgery. Where pressure on operating room time is great or the waiting list for cholecystectomy is long, the preferred approach should be simple cholecystectomy and endoscopic clearance.

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