Comparison of one stage laparoscopic cholecystectomy combined with intra-operative endoscopic sphincterotomy versus two-stage pre-operative endoscopic sphincterotomy followed by laparoscopic cholecystectomy for the management of pre-operatively diagnosed patients with common bile duct stones: a meta-analysis

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Abstract

Background Laparoscopic cholecystectomy (LC) for symptomatic gallstone disease is one of the most common surgical procedures. Concomitant common bile duct (CBD) stones are detected with an incidence of 4–20% and the ideal management is still controversial. The frequent practice is to perform endoscopic sphincterotomy pre-operatively (POES) followed by LC, to allow subsequent laparoscopic or open exploration if POES fails. However, POES has shown different drawbacks such as need for two hospital admissions, need of two anesthesia inductions, higher rate of pancreatitis, and longer hospital stay. Hence, an intra-operative endoscopic sphincterotomy (IOES) has been proposed.

Objective To compare the 1 stage laparoscopic cholecystectomy (LC) combined with IOES versus 2-stage POES followed by LC for the management of pre-operatively known cholecystocholedolithiasis.

Search strategy The search terms bile duct stones/calculi, ERCP, endoscopic sphincterotomy, laparoendoscopic rendezvous (LERV), and laparoscopic ductal clearance/choledochotomy/exploration were used. 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.

Selection criteria RCTs comparing 1 stage LC combined with IOES versus 2-stage POES followed by LC for the management of pre-operatively known cholecystocholedolithiasis in adults.

Data collection & analysis Three reviewers assessed trial quality and extracted the data. Data were entered in revman version 5.3. The trials were grouped according to the outcome measure assessed such as success rate of CBD stone clearance, incidence of pancreatitis, overall morbidity, and length of hospital stay.

Main results A total of 629 patients in 5 RCTs met the inclusion criteria. The success rate of CBD clearance (IOES = 93%, POES = 92%) was the same in both groups (OR 1.34; 95% CI 0.45–0.97; p = 0.60). Findings showed that IOES was associated with less pancreatitis (0.6%) than POES (4.4%) (OR 0.19; 95% CI 0.06–0.67; p = 0.01; I² = 43%). The incidence of overall morbidity was lower in the IOES group (6%) than the POES group (11%) (OR 0.54; 95% CI 0.31–0.96; p = 0.03; I² = 20%). The mean days of hospital stay for IOES group (M = 3.52, SD = 1.434, N = 5) was significantly less than the POES group (M = 6.10, SD = 2.074, N = 5), t(8) = 2.29, p = 0.051.

Conclusion IOES is at par with two-stage POES in terms of CBD clearance, with less incidence of post-operative pancreatitis, overall morbidity, and less hospital stay.

Keywords Common bile duct stones · Laparoendoscopic Rendezvous · Endoscopic Retrograde Cholangiopancreatography
**Background**

Common bile duct (CBD) stones are present in patients presenting with indications for cholecystectomy with a wide range of incidence (Reported range: 4–10% [1–4], 3.4–7.2% [5, 6], and 11–20% [7–9]). Of more concern is the management of these CBD stones, which had been debated for years since the introduction of laparoscopic cholecystectomy in the late 1980s [10–15].

In the era of open cholecystectomy, intra-operative cholangiography (IOC) was routinely done and detection of CBD stones resulted in exploration of the CBD and placement of T-tube [16]. With the advent of laparoscopy and endoscopy, followed by standardization of laparoscopic cholecystectomy (LC) as the gold standard in the management of symptomatic gallstone disease, there was a move away from the surgical management of CBD stones towards endoscopy [17]. Algorithms were developed to predict the presence of CBD stones pre-operatively, and to select the best treatment for the patient [18–23]. Management options were primarily endoscopic retrograde cholangiopancreatography (ERCP) before or after LC, which led to a specific concern in the timing of the endoscopic treatment of CBD stones in conjunction with surgery, as this was done as a two-stage procedure [24].

As surgeons developed the skills for advanced laparoscopic procedures, performing laparoscopic common bile duct exploration (LCBDE) became an option. This was done either transcystic (choledochoscopy) or transductal (choledochotomy), which are both technically demanding, hence done only in few centers [25].

With more treatment options at hand, came the debate for one versus two-stage management of CBD stones [26]. One stage pertaining to removing the gallbladder and CBD stones under one session of anesthesia induction. Two stage pertains to doing the procedure on two different occasions, addressing the CBD stones, followed by removal of the gallbladder on a separate anesthesia induction, or vice versa. Meta-analysis study done by Alexakis et al. had shown that both are at par in terms of success rate and morbidity, but the study generalized the one stage option as LCBDE and LC combined with intra-operative endoscopic sphincterotomy (IOES) [27]. With only two studies of IOES included out of the nine for one stage, the advantage of IOES may have been masked.

Numerous studies comparing specific one stage procedure IOES to the sequential two-stage pre-operative endoscopic sphincterotomy (POES) followed by LC has been published concluding that IOES has less morbidity and incidence of pancreatitis. What follows is a meta-analysis of these studies.

This meta-analysis study will determine the success rate of the one stage laparoendoscopic management of CBD stones. The data that will be collected and analyzed, will help us understand better the advantages and disadvantages of the timing of endoscopic sphincterotomy in relation to laparoscopic cholecystectomy. This will help laparoscopic surgeons as well as gastroenterologist in deciding which approach will be best for the patient, promoting early recovery, less hospital stay, with the lowest risks of complications.

**Objectives**

**General objective**

To compare the 1 stage LC combined with IOES versus 2-stage POES followed by LC for the management of pre-operatively known CBD stones.

**Specific objectives**

To compare the following between 1-stage IOES and 2-stage POES followed by LC in terms of:

1. Success rate of CBD stone clearance.
2. Rate of post-operative pancreatitis.
3. Overall Morbidity.
4. Length of hospital stay.

**Methodology**

**Research design: meta-analysis**

Criteria for considering studies for this review.

**Types of studies**

All trials were considered when the intention to assign the participants randomly to 1 stage LC combined with IOES and 2-stage POES followed by LC were done and published in english.

**Types of participants**

The review included trials wherein the participants were diagnosed pre-operatively with CBD stones, neither in cholangitis nor pancreatitis.
Types of interventions

Trials were considered if they compared 1 stage LC combined with IOES and 2-stage POES followed by LC.

Types of outcome measures

Trials were considered if any one of the following clinical outcomes were shown:
1. Success rate of CBD stone clearance.
2. Rate of post-operative pancreatitis.
3. Overall Morbidity.
4. Length of hospital stay.

Search Strategy

All randomized controlled trials citing 1 stage laparoscopic cholecystectomy (LC) combined with intra-operative endoscopic sphincterotomy (IOES) versus 2-stage pre-operative endoscopic sphincterotomy (POES) followed by LC for the management of pre-operatively known CBD stones in adults were identified by conducting an electronic search of the Surgical Endoscopy, Annals of surgery, and pubmed databases using the following keywords: bile duct stones/calculi, ERCP, endoscopic sphincterotomy, laparoendoscopic rendezvous (LERV), laparoscopic ductal clearance/choledochotomy/exploration. A comprehensive hand-based search of reference lists of published articles and pubmed databases using the following keywords: bile duct stones/calculi, ERCP, endoscopic sphincterotomy, laparoendoscopic rendezvous (LERV), laparoscopic ductal clearance/choledochotomy/exploration. A comprehensive hand-based search of reference lists of published articles and review articles was perform to ensure inclusion of all possible studies and exclude duplicates. Included are only documents published in English language up to the end of December 2013. Review articles, retrospective analyses and abstracts were not considered. After the search, we had 157 hits and the abstracts of these articles were reviewed. Only five articles were found to be pertinent to the review after methodological assessment.

Methods of the review

All potential trials were selected for eligibility according to the criteria specified in the protocol [28]. There were three reviewers whom extracted data from each publication. Discrepancies were resolved by the third reviewer who served as the arbiter. The quality of included studies was assessed independently by three reviewers using the Cochrane Handbook for Systematic Reviews of Interventions including random sequence generation, allocation concealment, blinding of the patient and observer, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each Trial included was approved by the ethics committee of their corresponding institution.

The main comparison of the 1 stage LC combined with IOES and 2-stage POES followed by LC was stratified by outcome.
1. Success rate of CBD stone clearance.
2. Rate of post-operative pancreatitis.
3. Overall Morbidity.
4. Length of hospital stay.

Statistical analysis

The odds ratio (OR) was the primary measure of treatment effect or adverse events, and 95% CIs for OR were calculated. Heterogeneity was assessed by Q-square ($\chi^2$) and I-square statistics ($I^2$) [13]. The $I^2$ statistic indicated the percentage variability due to between-study (or interstudy) variability as opposed to within-study (or intrastudy) variability. An $I^2$ value greater than 50% was classified as a substantial presence of heterogeneity [13].

Studies were combined using the fixed-effects model when heterogeneity could be considered low and using the random-effects model described by DerSimonian and Laird when $I^2$ was greater than 50% [29]. Meta-analysis with forest plot was performed using Review Manager Version 5.3. For length of hospital stay, a preliminary test for the equality of variances indicates that the variances of the two groups were not significantly different $F = 2.178$, $p = 0.269$. Therefore, a two-sample $t$ test was performed assuming equal variances.

The MECIR (Methodological Expectations of Cochrane Intervention Reviews) standard was also applied using the five GRADE (Grading of Recommendations Assessment, Development and Evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to further assess the quality of the body of evidences for each outcomes.

Results

Five RCTs were included in the meta-analyses. These are summarized in Table 1 [30–34]. The five studies included a total of 629 patients.

Assessment of quality according to the Cochrane Collaboration’s tool for assessing risk of bias for RCTs is reported in Fig. 1 below.

Table 2: Summary of findings (v2) (https://gdt.guidelinedevelopment.org/)

Success rate of CBD clearance

The success rate of CBD clearance for IOES was at 293 out of 313 subjects (93%) which is at par with POES with 292
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Time of recruitment</th>
<th>Major inclusion criteria &amp; exclusion criteria</th>
<th>Outcomes</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lella et al.</td>
<td>2006</td>
<td>Jan 2002 to Sep 2004</td>
<td>US and MRI Diagnosis of CBD stone No previous sphincterotomy No cholangitis and pancreatitis</td>
<td>CBD clearance rate Post-ERCP pancreatitis Duration of procedures Length of hospital stay Total Morbidity</td>
<td>NA</td>
</tr>
<tr>
<td>Morino et al.</td>
<td>2006</td>
<td>May 2001 to Aug 2005</td>
<td>US diagnosis of CBDS or bile duct dilation Elevated liver function tests No cholangitis No pancreatitis No previous cholecystectomy No contraindication to laparoscopy</td>
<td>CBD clearance rate Operative time Conversion rate Intra-operative and post-operative morbidity Post-operative pancreatic enzymes 60-Day mortality Length of hospital stay</td>
<td>Mean follow-up, 19 months; range 6–50 months</td>
</tr>
<tr>
<td>Rabago et al.</td>
<td>2006</td>
<td>June 1999 to June 2003</td>
<td>US diagnosis of CBDS or bile duct dilation Elevated liver function tests No contraindication to laparoscopy No pancreatitis Not in cholangitis</td>
<td>CBD clearance rate Intra-operative and post-operative morbidity Post-ERCP pancreatitis Costs Hospital Stay</td>
<td>24 months</td>
</tr>
<tr>
<td>ElGeidie et al.</td>
<td>2011</td>
<td>June 2006 to Sept 2009</td>
<td>US diagnosis of CBDS or bile duct dilation Elevated liver function tests No cholangitis or pancreatitis No contraindications to laparoscopic surgery as previous upper abdominal surgery and marked liver cirrhosis</td>
<td>Operative time Conversion rate Intra-operative &amp; post-operative morbidity 60-day mortality Length of hospital stay Failure of ERCP Complications of ERCP (including pancreatitis, perforation, and bleeding) Complications of LC (bile duct lesions, bleeding, abdominal collections, pneumoniae, organ failure, etc.).</td>
<td>NA</td>
</tr>
<tr>
<td>Tzovaras et al.</td>
<td>2012</td>
<td>Sept 2006 to April 2009</td>
<td>MRI diagnosis of CBDs No previous ERCP Patients at high risk of choledocholithiases No cholangitis or pancreatitis</td>
<td>Hospital length of Stay Intra-operative and post-operative morbidity Post-operative pancreatic Enzymes Success rate of CBD clearance</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Fig. 1** Risk of bias graph: review of authors’ judgements about each risk of bias item presented as percentages across all included studies.
Table 2 shows summary of findings done from GRADEpro which assessed the evidences for each outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (studies) follow-up</th>
<th>Quality of the evidence (Grade)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with POES</th>
<th>Risk difference with IOES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate of CBD clearance</td>
<td>630 (5 RCTs)</td>
<td>MODERATE</td>
<td>OR 1.34 (0.45–3.97)</td>
<td>921 per 1000</td>
<td>19 more per 1000 (81 fewer to 58 more)</td>
<td></td>
</tr>
<tr>
<td>Post-operative pancreatitis</td>
<td>629 (5 RCTs)</td>
<td>HIGH</td>
<td>OR 0.19 (0.06–0.67)</td>
<td>44 per 1000</td>
<td>36 fewer per 1,000 (42 fewer to 14 fewer)</td>
<td></td>
</tr>
<tr>
<td>Overall morbidity</td>
<td>629 (5 RCTs)</td>
<td>HIGH</td>
<td>OR 0.54 (0.31–0.95)</td>
<td>117 per 1000</td>
<td>50 fewer per 1000 (78 fewer to 5 fewer)</td>
<td></td>
</tr>
</tbody>
</table>

GRADE working group grades of evidence

*High quality* We are very confident that the true effect lies close to that of the estimate of the effect

*Moderate quality* We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

*Low quality* Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

*Very low quality* We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI Confidence interval, OR Odds ratio

* Heterogeneity was moderate with I-square value more than 50%. This is due to differences in technical expertise of the rendezvous technique across studies

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** CBD clearance rates after IOES and POES showing no statistical significant advantage ($p = 0.59$)

out of 316 (92%). Pooled analysis of 5 studies (630 participants) found OR of 1.34 (95% CI 0.45–0.97; $p = 0.60$)(Fig. 2). There is no serious concern with the risk of bias, but the heterogeneity($I^2 = 56\%$) across studies was moderately high. There were no indirectness, imprecision, nor detected publication bias. Overall, the quality of the evidence is moderate (Table 2).

*Conclusion* IOES appears to be at par with POES in terms of CBD clearance success rate.

**Rate of Post-operative Pancreatitis.**

The outcome of rate of post-operative pancreatitis for IOES was at 2 out of 313 subjects (0.006%) compared to POES with 14 out of 316 (0.04%). The difference between the two group was statistically significant, favoring IOES. Pooled analysis of 5 studies (629 participants) found OR of 0.19 (95% CI, 0.06–0.67; $p = 0.01$)(Fig 3). There is no serious concern with the risk of bias or heterogeneity($I^2 = 43\%$). There were no indirectness, imprecision, nor detected publication bias. Overall, the quality of the evidence is high (Table 2).

*Conclusion* IOES has less post-operative pancreatitis than POES.

**Overall morbidity**

The outcome of overall morbidity for IOES was at 21 out of 313 subjects (0.06%) compared to POES with 37 out of 316 (0.11%). The difference between the two group was statistically significant, favoring IOES. Pooled analysis of 5 studies (629 participants) found OR of 0.54 (95% CI, 0.31–0.95; $p = 0.01$)(Fig 3). There is no serious concern with the risk of bias or heterogeneity($I^2 = 56\%$). There were no indirectness, imprecision, nor detected publication bias. Overall, the quality of the evidence is high (Table 2).
statistically significant, favoring IOES. Pooled analysis of five studies (629 participants) found OR of 0.54 (95% CI 0.31–0.95; \( p = 0.03 \))(Fig. 4). There is no serious concern with the risk of bias or heterogeneity(\( I^2 = 19\% \)). There were no indirectness, imprecision, nor detected publication bias. Overall, the quality of the evidence is high (Table 2).

**Conclusion** IOES has less overall morbidity than POES.

**Length of hospital stay**

Average hospital stay was less in the IOES (3.5 days) compared to POES (6.1 days). Using two-sample \( T \) test assuming equal variances, the mean days of hospital stay for IOES (\( M = 3.52, \) SD = 1.434, \( N = 5 \)) was significantly less than those for POES (\( M = 6.10, \) SD = 2.074, \( N = 5 \)), \( t(8) = 2.29, \) \( p = 0.051 \).

**Discussion**

Stones in the CBD most commonly result from the passage of gallstones through the cystic duct into the CBD. As high as 18% of patients undergoing cholecystectomy for gallstones have concomitant CBD stones [14], and up to 3.8% have symptoms related to CBD stones during the first year after cholecystectomy [35].

The standard management of CBD stones before was open cholecystectomy, IOC, and proceeding to CBD exploration if stones were detected. After the technological development of accurately detecting CBD stones pre-operatively, with CT scan or magnetic resonance cholangiopancreatography (MRCP), ERCP became a management option. With ERCP as an armamentarium in the management of CBD stones, patients currently are managed in a two-stage procedure, with pre- or post-operative ERCP and LC.

CBD stone clearance was found to be as effective as pre-operative (OR 1.00 95% CI 0.53–1.80) and post-operative ERCP (OR 2.27, 95% CI 0.37–13.9), with no significant difference in morbidity and mortality [14]. However, current trend favors the sequential 2-stage ERCP followed by LC. As in a logical sense, this will ensure that if the pre-operative ERCP fails, CBD stones can still be managed on the 2nd stage which is during LC. On the other hand, the option of LC followed by ERCP may result to more than two stages, when ERCP fails to remove the CBD stones after LC.

Several problems arise with the 2 stage approach. Despite the different predictive models used to stratify patients’ risk for CBD stones, patients stratified as high risk even in the presence of clinical, laboratory, and imaging indicators, who underwent ERCP are found to have CBD stones only 32% of the time [36]. This makes ERCP a diagnostic procedure with risk of pancreatitis (1–30%), pancreatic necrosis (0.3–0.6%), and mortality (0.4%) which is unacceptable [37]. Then another decision making...
process in this 2 stage approach commonly debated is the timing of the LC after the ERCP. Recommendations across different literatures ranges from 24 to 72 h up to 6 weeks, and this delay leads to the 10% risk of recurrent CBD stones in these patients [38]. Other disadvantages are increase hospital stay and costs (sometimes 2 hospital admission), loss of compliance, and increased conversion rate for LC (20%). [39, 40–44].

This led us to the possible advantages of the one stage approach in the management of CBD stones. With increasing laparoscopic and endoscopic expertise, one stage can be done either LC + LCBDE (transcystic or transductal), or one stage laparoscopic/endoscopic management. Kenny R. et al. reviewed several meta-analysis studies comparing the advantages of one stage LC +LCBDE to the 2 stage ERCP + LC, which showed equivalent clinical complications but better cost-effectiveness due to reduced length of hospital stay. The paper concluded LC + LCBDE to be the preferred procedure where resources and local expertise are available. [45] This study highlights the advantage of LC + LCBDE as a one stage procedure, not the advantage of LCBDE as the surgical technique itself.

Our paper aimed at investigating the other option of one stage which is LC + IOES which targets the major drawback of ERCP being a 2 stage procedure, and at the same time, most of our surgeons and gastroenterologist are more versed in LC and ERCP than the LCBDE. One of the important factor only needed to be established is the logistics and collaboration between the two departments. Despite its’ advantages being a one stage approach, the combined procedure of laparoscopy and endoscopy in the management of CBD stones may shorten the operative time with less morbidity.

In our study, the one stage IOES is at par with POES in terms of CBD clearance success rate, and is statistically superior in reducing perioperative complications such as bleeding, perforation, and pancreatitis as well as pancreatitis alone. Considering that these unfavorable outcomes may lead to severe disease progression and a longer hospital stay, the lower rate of complications and pancreatitis, could be interpreted as a potential advantage. However, the paucity of studies and included patients still limit the strength of our findings.

There are several advantages of IOES compared with the two-stage approach. IOES results in a reduction of anesthetic procedures, hospital stay, and total costs [46, 47]. Del Rio et al. noted that these factors improved patients’ compliance and eliminates possible patient drop out occurring when two-stage approach require two different hospital admission [48]. Another is IOES eliminates the problem concerning the proper timing between ERCP and LC, with possible recurrent biliary complications to patients who do not undergo LC after POES within short interval [39]. Moreover, different studies have shown that LC is more difficult after POES, due to disruption of Oddi’s Sphincter and bacterial colonization of biliary tract leading to inflammation and scarring of hepatoduodenal ligament hindering dissection of Calot’s triangle [49]. Finally, it minimizes the risks related to ERCP avoiding its critical phases of retrograde inadvertent cannulation of pancreas and papillary manipulation [50, 51].

Despite the advantages of IOES, there are several limitations. IOES is challenging because of the position of the patient on the operative table and the need of endoluminal insufflation for endoscopic vision. There is difficulty of CBD cannulation for inexpert endoscopist for during IOES, patient is in supine position and requires an extra-rotation by the endoscopist in order to achieve a correct alignment between the sphincterotome and the CBD axis.

Another principal factor hindering the application of IOES seems related mainly to logistical and organizational problem [52, 53]. Two different teams (Surgical and endoscopic) and equipment are needed to be present in the operating theater at the same moment requiring a high level of collaboration.

In the studies included, limited heterogeneity were observed, but few RCTs have been published to date. The uptake of one stage IOES is limited because published studies disproportionately reflect the experience of “pioneering” surgical centers, which may achieve better success rates than standard centers. On the other hand, these studies represent the experience of centers in a range of different countries and health care systems [54].

We conclude that IOES is a better option than POES in the management of pre-operatively diagnosed CBD stones. This approach is a single-stage treatment that reduces the rate of post-operative pancreatitis and overall morbidity. It also eliminates the need to return to the operating room following technical failure of ERCP. However, the best treatment choice for any patient with CBDS must be based on locally available expertise and resources.

Compliance with ethical standards

Disclosures Doctors Chester C. Tan, Omar Ocampo, Raymund Ong, and Kim Shi Tan have no conflicts of interest or financial ties to disclose.

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