Laparoendoscopic rendezvous reduces perioperative morbidity and risk of pancreatitis

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Abstract
Background
The ideal management of cholelithiasis and common bile duct stones still is controversial. Although the two-stage sequential approach remains the prevalent management, several trials have concluded that the so-called laparoendoscopic rendezvous (LERV) technique offers some advantages, such as a reduced risk of post-ERCP (endoscopic retrograde cholangiopancreatography) pancreatitis. This study aimed to compare the single-stage LERV technique with the two-stage endoscopic sphincterotomy followed by laparoscopic cholecystectomy.
Methods
A search for randomized controlled trials (RCTs) comparing LERV and the two-stage sequential approach was conducted. The outcomes considered were overall complications and pancreatitis. Medline, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1998 to July 2012. Odds ratios (ORs) were extracted and pooled using a fixed or random-effect model depending on I^2 used as a heterogeneity measure.
Results
Four RCTs, including a total of 430 patients, met the inclusion criteria. The incidence of overall complications was lower in the LERV group (11.2 %) than in the two-stage intervention group (18.1 %) (OR, 0.56; 95 % confidence interval [CI], 0.32–0.99; P = 0.04; I^2 = 45 %). The findings showed that LERV was associated with less clinical pancreatitis (2.4 %) than the two-stage technique (8.4 %) (OR, 0.33; 95 % CI, 0.12–0.91; P = 0.03; I^2 = 33 %).
Conclusions
Despite the limitation of a small number of studies completed, the evidence of RCTs shows that LERV is superior to two-stage treatment due to a reduction in overall complications, particularly pancreatitis.
Keywords
Common bile duct Gallbladder Laparoendoscopic rendezvous Metaanalysis Stones Systematic review
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The prevalence of common bile duct stones (CBDS) in patients with gallstones varies widely depending on several clinical and radiologic findings, but usually ranges from 11 to 20 % [*1–3*]. About half of the asymptomatic CBDS discovered accidentally at intraoperative cholangiography would pass the papilla of Vater spontaneously within the following 6 weeks [*4*]. However, stones might be retained and cause cholangitis, hepatic abscess, and pancreatitis, justifying an invasive approach.
Since the introduction of laparoscopic cholecystectomy (LC) in the early 1990s, given the large number of possible strategies, the ideal management of CBDS for patients affected by gallstones

disease still is a matter of debate [*5*]. Because laparoscopic common bile duct exploration still is considered a highly demanding procedure, alternative strategies and techniques have been proposed over the years.

The sequential approach, represented by a preoperative endoscopic sphincterotomy (ES) (two-stage intervention), is widely used and remains the reference treatment for such disease. Given the increased number of procedures per patient associated with this strategy compared with a single-stage intervention [*5*], the morbidity and the risk of iatrogenic damage associated with perioperative ES [*6*], the so-called laparoendoscopic rendezvous (LERV), is recently gaining acceptance. This technique allows an easier cannulation of the common bile duct to perform ES. This supposedly allows a higher rate of CBDS clearance to be achieved with lower morbidity.

We aimed to identify and describe all randomized controlled trials (RCTs) comparing single-stage LERV with preoperative ES followed by cholecystectomy (two-stage approach), and to evaluate the effectiveness of the two procedures in reducing perioperative complications and pancreatitis. This short report moves from the protocol of a Cochrane systematic review currently used and reports the preliminary findings.

Methods

Eligibility criteria

The study selection was limited to RCTs, regardless of their language and publication status. Only patients undergoing LERV, as described by Cavina et al. [*7*], were eligible to be part of the intervention group. Anterograde sphincterotomy and nonaided intraoperative retrograde cholangiopancreatography were excluded intentionally. In the comparison group, we included only preoperative ES followed by LC. No restriction was imposed on the timing of the subsequent operation.

Outcomes

For this short report, we considered overall perioperative complications defined as procedural bleeding, perforation, and postoperative pancreatitis defined as pancreatic-like pain persisting at least 24 h after endoscopic retrograde cholangiopancreatography (ERCP) associated with a significant increase in serum amylase levels.

Search strategy

We searched the Cochrane Hepatobiliary Group Controlled Trials Register [*8*], the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, the Science Citation Index Expanded [*9*], and the World Health Organization International Clinical Trials Registry Platform (ICTRP). Moreover, to minimize publication bias, the U.S. National Institutes of Health (NIH) trial registry (ClinicalTrials.gov) also was examined for potentially relevant unpublished results. Because LERV was first standardized in 1998 [*7*], the search was limited to the years after 1998.

The preliminary search strategy included the term “rendezvous.” All abstracts retrieved from electronic databases were screened by two independent reviewers, and for each abstract deemed relevant by at least one person, the full text was obtained. The reference lists of potentially relevant articles were screened for further potentially relevant citations.

Risk of bias assessment

The quality of included studies was assessed independently by two authors using the Cochrane Handbook for Systematic Reviews of Interventions including allocation sequence generation, allocation concealment, blinding of the patient and observer, incomplete outcome data, and selective outcome reporting.

Data collection, statistical analysis, and selection of studies

The odds ratio (OR) was the primary measure of treatment effect or adverse events, and 95 % confidence intervals (CIs) for OR were calculated. Heterogeneity was assessed by Q-square (χ^2) and I-square statistics (I^2) [*10*]. 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 [*10*].
We combined the studies 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 % [*11*]. All analyses were performed according to the recommendations of the Cochrane Collaboration [*10*]. We used the metaanalyses RevMan 5 software [*12*].
We performed a sensitivity analysis to determine whether findings were sensitive to restriction of the analyses to studies judged to have low risk of bias for generation of the allocation sequence of the primary outcome.

Results

Study selection and characteristics

The search retrieved 327 articles. Exclusion of duplicates and irrelevant references left 53 records, whose abstracts were analyzed in more detail. We excluded 28 studies because they considered different interventions (e.g., intraoperatory ERCP without rendezvous, comparison with laparoscopic choleductolithotomy). We analyzed the full text of the remaining 24 studies and excluded 16 case series without control groups and 4 nonrandomized controlled trials.
Four RCTs were included in the metaanalyses. These are summarized in Table 1 [*13–16*]. The four studies included a total of 430 patients. Assessment of quality according to the Cochrane Collaboration's tool for assessing risk of bias for RCTs is reported in Table 2.
Table 1
Characteristics of the studies included in the analysis

Author	**Year**	**Time of recruitment**	**Country**	**Major inclusion and exclusion criteria**	**Other cointerventions**	**Outcomes**	**Duration of follow-up**
Lella et al. [*15*]	2006	Jan 2002 to Sept 2004	Italy	US and MRI diagnosis of CBDS No chronic pancreatitis No previous sphincterotomy	None	Post-ERCP pancreatitis (pancreatic-like pain persisting at least 24 h after ERCP associated	NA

Author	Year	Time of recruitment	Country	Major inclusion and exclusion criteria	Other cointerventions	Outcomes	Duration of follow-up
						with serum amylase levels more than five times the upper normal limit) Duration of the procedures Hospital stay	
Morino et al. [*13*]	2006	May 2001 to Aug 2005	Italy	US diagnosis of CBDS or bile duct dilation Elevated liver function tests No cholangitis No pancreatitis No previous cholecystectomy No contraindication to laparoscopy	None	Operative time Conversion rate Intraoperative and post-operative morbidity Postoperative pancreatic enzymes 60-Day mortality Length of hospital stay	Mean follow-up, 19 months; range, 6–50 months
Rábago et al. [*16*]	2006	June 1999 to June 2003	Spain	US diagnosis of CBDS or bile duct dilation Elevated liver function tests No contraindication to laparoscopy No chronic pancreatitis	None	Intraoperative and post-operative morbidity Costs	24 months
Tsovaras et al. [*14*]	2012	Sept 2006 to April 2009	Greece	US or MRI diagnosis of CBDS BMI >35 Previous ERCP	None	Hospital length of stay Intraoperative and post-operative morbidity Post-operative pancreatic	NA

Author	Year	Time of recruitment	Country	Major inclusion and exclusion criteria	Other cointerventions	Outcomes	Duration of follow-up
						enzymes Success rate of CBD clearance	

US abdominal ultrasound, MRI magnetic resonance cholangiopancreatography, CBDS common bile duct stones, ERCP endoscopic retrograde cholangiopancreatography, NA not available

Table 2

Quality assessment for randomized controlled trials (RCTs) according to the Cochrane Collaboration's tool for assessing risk of bias

Author	Year	Allocation sequence generation	Allocation concealment	Blinding (patient)	Blinding (observer)	Incomplete outcome data	Selective outcome reporting	Other source of bias
Lella et al. [*15*]	2006	Low risk	Low risk	High risk	High risk	Uncertain risk	Low risk	None
Morino et al. [*13*]	2006	Low risk	Low risk	High risk	High risk	Uncertain risk	Low risk	None
Rábago et al. [*16*]	2006	Low risk	Low risk	High risk	High risk	Uncertain risk	Low risk	None
Tsovaras et al. [*14*]	2012	Low risk	Low risk	High risk	High risk	Uncertain risk	Low risk	None

Overall perioperative complications

Complications including bleeding, perforation, and pancreatitis occurred for 24 (11.2 %) of 214 patients in the LERV group and for 39 (18.1 %) of 216 patients in the two-stage group. The overall OR was 0.56 (95 % CI, 0.32–0.99; P = 0.04), favoring the LERV group. Heterogeneity was moderate (I^2 = 45 %) (Fig. 1).

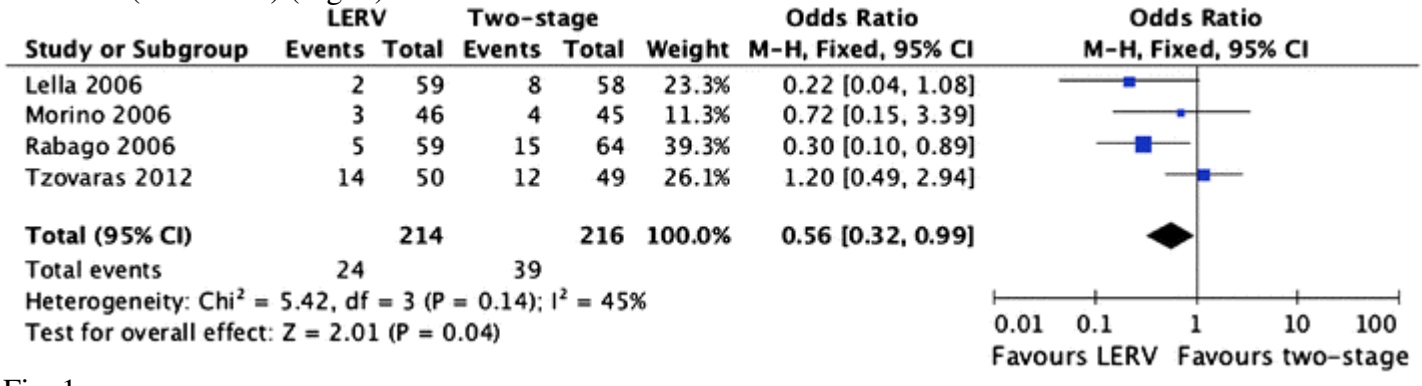

Fig. 1

Perioperative complication rates after laparoendoscopic rendezvous (LERV) and two-stage treatment, showing a statistically significant advantage of LERV (P = 0.04)

Pancreatitis

Only three trials, evaluating 331 participants, reported the incidence of post-ERCP pancreatitis [*13–15*]. The event was recorded for 4 (2.4 %) of 164 patients in the LERV group and for 14 (8.4 %) of 167 patients in the two-stage group. The difference between the two groups was statistically significant, favoring the LERV group. The OR was 0.33 (95 % CI, 0.12–0.91; P = 0.03), with limited heterogeneity (I^2 = 33 %) (Fig. 2).

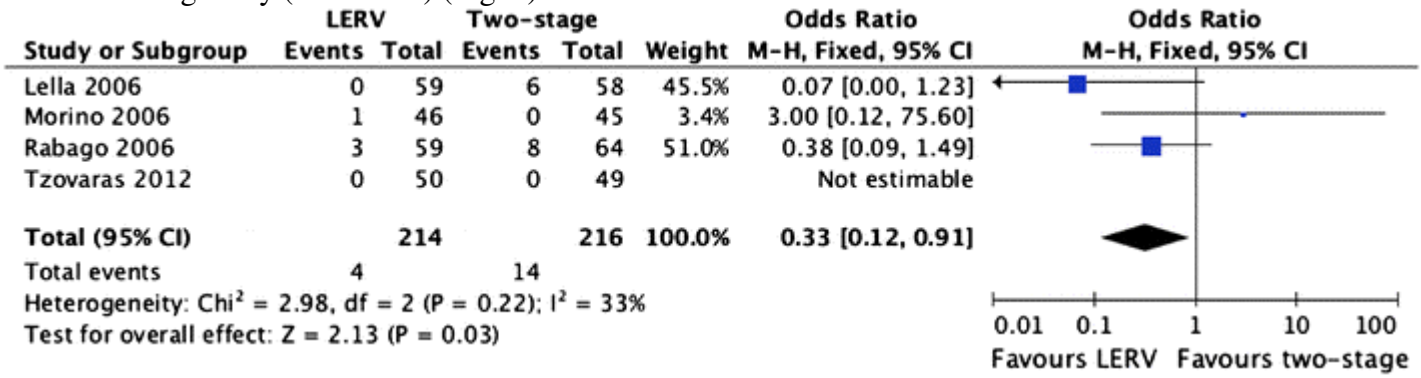

Fig. 2
Post-ERCP rates of pancreatitis after laparoendoscopic rendezvous (LERV) and two-stage treatment, showing a statistically significant advantage of LERV (P = 0.03). ERCP endoscopic retrograde cholangiopancreatography

Discussion

The evidence favoring LERV over two-stage treatment for cholelithiasis and CBDS is promising. Our primary finding was that the LERV procedure is statistically superior to the two-stage procedure in reducing perioperative complications such as bleeding, perforation, and pancreatitis as well as pancreatitis alone. Considering that these unfavorable outcomes are frequent and may lead to severe disease progress 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.

The correct timing of ES for cholelithiasis and CBDS in patients undergoing LC has been a matter of debate in recent years. Four RCTs were identified by our systematic review. Three of the four RCTs had overall perioperative complications as a primary outcome. Two of the RCTs could demonstrate an advantage of the LERV technique in terms of a lower risk for pancreatitis, whereas the remaining RCTs concluded that the LERV technique achieved a higher rate of common bile duct clearance and a shorter hospital stay.

It seems that LERV is associated with a higher therapeutic success rate than either preoperative ES or laparoscopic bile duct exploration [*6*] and that it is considered easier to perform than standard ES by the majority of endoscopists [*17*].

Despite the advantages of LERV, several limitations need to be mentioned. First, intraoperative ES during the LERV technique is challenging because it needs to combine the necessities of two different teams, the surgical and the endoscopic necessities, including the position of the patient on the operative table and the need of endoluminal insufflation for endoscopic vision. This implies a longer operative time (of about 60 min) than for LC alone [*18*] and a longer hospital stay for the preoperative workflow [*14*].

Second, patients previously treated by total or partial gastric resection are unlikely to be suitable for a rendezvous procedure. Third, giant impacted stones, Mirizzi syndrome, and periampullary diverticula are other described limitations [*13*, *14*, *19*]. Fourth, an overall complications rate reaching 11 %, including postsphincterotomy bleeding, cystic duct leak, and pancreatitis, even if lower than with the two-stage procedure, still needs to be considered. Finally, LERV requires availability of the endoscopic team, which rarely belongs to the same unit, raising organization issues.

Nevertheless we decided, while preparing the extensive protocol and results of the Cochrane review, to communicate these preliminary findings to confirm the role of single-stage LERV for the treatment of CBDS in patients scheduled for LC as the potential procedure of choice.

It is difficult to assess how these results are applicable in different environments. We observed limited heterogeneity between studies, but few RCTs have been published to date. The uptake of LERV 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.

Future trials are expected to confirm the advantage of LERV over two-stage treatment in terms of both peroperative complications and post-ERCP pancreatitis alone while addressing other important issues such as cost analysis and quality of life assessment offered by the two techniques.

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