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Meta-analysis of the efficacy of a single stage laparoscopic management versus two-stage endoscopic management of symptomatic gallstones with common bile duct stones.

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META-ANALYSIS OF THE EFFICACY OF A SINGLE-STAGE LAPAROSCOPIC MANAGEMENT VERSUS TWO-STAGE ENDOSCOPIC MANAGEMENT OF SYMPTOMATIC GALLSTONES WITH COMMON BILE DUCT STONES

Meta-analiza učinkovitosti laparaskopskog liječenja u jednom aktu u usporedbi s endoskopskim liječenjem simptomatskih žučnih kamenaca i žučnih kamenaca u glavnom žučovodu u više akata

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Abstract

Background. The optimal treatment of gallstones with associated common bile duct stones in the laparoscopic era is controversial. Various reviews and decision based algorithms have been published, but the superior treatment modality is unclear. Therefore, a meta-analysis was conducted to compare the two most commonly used treatment strategies.

Methods. A systematic review was conducted to compare single stage laparoscopic cholecystectomy with common bile duct exploration versus a combined endoscopic and laparoscopic treatment. Eligible studies were identified using a search of Medline, Embase, Cochrane and Science Citation Index Expanded databases. Appropriately selected articles were independently reviewed and data was extracted and cross referenced. A meta-analysis was conducted of the pooled trial data to determine difference in outcomes.

Results. A total of seven randomized trials were identified with 746 patients with 366 in the laparoscopic only treatment group and 380 in the combined endoscopic and laparoscopic treatment arms. There was no significant difference in successful bile duct clearance between the two groups (OR 1.23; 95% CI 0.55 to 2.75, P = 0.61). There was no statistical difference in morbidity (RR 1.23; 95% CI 0.92 to 1.66; P = 0.17), mortality (RD -0.00; 95% CI -0.02 to 0.01, P = 0.59) or length of hospital stay (MD -0.31; 95% CI -1.68 to 1.06, P = 0.66). However, there was a statistically significant difference in the duration of procedure in favour of the single stage laparoscopic treatment (MD -6.83; 95% CI -9.59 to -4.07, P < 0.00001).

Conclusion. Both the laparoscopic alone or the combined endoscopic and laparoscopic treatment approaches show comparative efficacy in management of symptomatic gallstones with associated choledocholithiasis.

Keywords

gallstones, choledocholithiasis, cholecystectomy, laparoscopic, endoscopic retrograde cholangiopancreatography

Sažetak

Pozadina. Optimalno liječenje žučnih kamenaca uz prateće žučne kamence u glavnom žučovodu u eri laparoskopske kirurgije je kontroverzno. Objavljeni su razni pregledni radovi i algoritmi odlučivanja, no pitanje odluke o odabiru preporučenog načina liječenja ostaje neriješeno. S ciljem usporedbe dva najčešće korištena načina liječenja provedena je meta-analiza.

Metode. Sistematsko istraživanje provedeno je kako bi se usporedila kolecistektomija s eksploracijom glavnog žučovoda u jednom aktu u odnosu na kombinirano endoskopsko i laparoskopsko liječenje. Dostupne studije nađene su pomoću sljedećih baza podataka: Medline, Embase, Cochrane i Science Citation Index Expanded. Probrani relevantni radovi zasebno su pregledani, a podaci izdvojeni i međusobno uspoređeni. Provedena je meta-analiza svih prikupljenih podataka da bi se odredila razlika u ishodima.

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Rezultati. Pronađeno je sveukupno sedam randomiziranih studija sa 746 pacijenata od kojih je 366 u skupini liječenoj isključivo laparoskopski te 380 liječenih kombinirano endoskopski i laparoskopski. Nije utvrđena značajna razlika u uspješnom čišćenju žučnih vodova između dvije skupine (OR 1,23; 95% CI 0,55 do 2,75, P = 0,61). Nije nađena značajna razlika u morbiditetu (RR 1,23; 95% CI 0,92 do 1,66; P = 0,17), smrtnosti (RD -0,00; 95% CI -0.02 do 0,01, P = 0,59) ili trajanju hospitalizacije (MD -0,31; 95% CI -1,68 to 1,06, P = 0,66). Međutim, postojala je statistički značajna razlika u trajanju zahvata (MD -6,83; 95% CI -9,59 do -4,07, P < 0,00001).

Zaključak. Laparoskopski ili kombinirani endoskopski i laparoskopski pristup liječenju pokazuje značajnu učinkovitost u liječenju simptomatskih žučnih kamenaca s pratećom koledoholitijazom.

Ključne riječi

žučni kamenci, koledoholitijaza, kolecistektomija, laparoskopski, endoskopska retrogradna kolangiopankreatografija

1. Introduction

Cholelithiasis and complications thereof are a common clinical entity as 5 to 25% of adults in western countries have gallstones [1]. Symptoms and complications related to gallstones are one of the most costly digestive disorders [2]. In addition, 10–15% of patients with gallstones have associated or suspected common bile duct (CBD) stones (choledocholithiasis) [3, 4] and several risk factors, including clinical, biochemical and imaging variables, can help predict the presence of CBD stones [4].

Endoscopic retrograde cholangiopancreatography (ERCP) combined with endoscopic sphincterotomy (ES) has a key role in the management of CBD stones. Successful clearance of CBD stones ranges between 87 to 97% depending on the experience of the endoscopist [5, 6]. ERCP has evolved from a diagnostic to a therapeutic procedure due to high rate of negative examinations, risk of complications and increasing availability of laparoscopic common bile duct exploration (LCDBE) [7, 8]. Other non-invasive or minimally invasive diagnostic techniques to detect CBD stones have also evolved [9–11], and it is therefore imperative to identify the most efficient and effective treatment strategy for CBD stones. Laparoscopic cholecystectomy (LC) has replaced open cholecystectomy as the standard treatment for gallbladder stones [12, 13], with successful common bile duct clearance rates in experienced hands exceeding 90% [3, 14, 15]. Therefore, with improved skill and advances in laparoscopic techniques and given the time frame of previous reviews, a comparison of the two approaches is essential to identify the most optimum method of treatment of symptomatic gallstones with associated CBD stones.

2. Materials and Methods

2.1. Study design

This review was conducted according to the PRISMA guidelines for systematic review reporting [16]. A quality assessment of each trial using the Cochrane collaboration tool for assessing the risk of bias was applied [17]. The design is a systematic review with meta-analysis of randomized controlled trials with no restriction on the year of publication, or language.

2.2. Inclusion and exclusion criteria

We included in this review randomized controlled trials comparing single stage laparoscopic exploration of CBD with LC to a two stage endoscopic with LC treatment irrespective of language, year of publication or patient populations in the primary studies. We excluded observational studies, review articles and other non-randomized trials comparing both interventions. Outcomes measured include; primary outcome – successful bile duct clearance of stones, secondary outcomes include – morbidity, mortality, length of hospital stay, duration of procedure and total hospital cost.

2.3. Search methods for identification of studies

The electronic data base searched till March 2012 includes The Cochrane Hepato-Biliary Group Controlled trials Register, Cochrane Central Register of Controlled Trials in the Cochrane Library, Medline (1950 to March 2012), Embase (1980 to March 2012), and Science citation index expanded database (1970 to March 2012). The following keywords: gallstones OR choledocholithiasis OR ("bile duct stones" AND cholecystectomy); laparoscopic OR choledochotomy; laparoscopic OR (laparoscopic AND "bile duct") AND (cholangiopancreatography endoscopic retrograde OR endoscopic sphincterotomy). These keywords were mapped to Medline medical subject heading (MeSH) terms as well as searched for as text items. A filter for identification of randomized controlled trials recommended by the Cochrane Collaboration was used to filter out non-randomized trials in Medline and Embase database. Hand searches of references of cited journals were conducted to also identify potential eligible articles to include in the review. Search of reputable international conference journals was also conducted to identify potential eligible papers.

2.4. Study selection and data extraction

A flow sheet was used to tract abstracts of identified, screened and eligible articles (Figure 1). Full text of eligible articles was independently reviewed by two investigators and required data of the outcomes needed to collate results was collected by two

independent investigators on a data extraction sheet. This is further synthesized into a comprehensive summary of randomized trials table comparing both treatment outcomes as shown in Table 1. For missing outcome data, a contact was made with the corresponding author by e-mail to obtain such additional information.

2.5. Quality assessment of included studies

There is a risk of over or under estimation of beneficial treatment effects in trials with high risks of bias [17]. Selected trials were graded for risk of bias at study level using the guidelines of the Cochrane collaboration tool for assessing risk of bias table and quality assessment [18]. The assessment was done on trials using the six main components of the tool such as; sequence generation, allocation concealment, blinding of participant, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias such as funding bias or early stopping bias. A score was given to each component of either "low risk", "unclear" or "high risk", and reasons for the score are included (Table 2). Three of the trials show low risk of bias in the parameters while the remaining studies are low risk in two parameters. The performance and detection bias were of high risk as there was no attempt of blinding in any trials though the outcomes are objectively measured but the impact on the results and trials quality may be difficult to predict.

2.6. Statistical methods

The software package Review Manager 5 [19] provided by the Cochrane Collaboration Version 5.1 (Copenhagen) was used for data analysis. For dichotomous outcomes, odds ratio or relative risk with 95% confidence interval was calculated using the Mantel-Haenszel statistical method for the meta-analysis. For data with zero events, risk difference was calculated; this was used for the mortality results. While for continuous outcomes, the mean difference with 95% confidence interval was used. In continuous outcomes, if mean and standard deviation were not given, the median and range can be used to estimate the mean and variance using the formula proposed by Hozo et al. [20], and the estimated result will be used for the meta-analysis.

For odds ratio and mean difference outcomes, we used the random-effects and fixed-effect models (e.g. see Figure 2). If there are no differences between the results of the two models, the fixed effect model will be reported. If differences exist in the intervention effects, both the random and fixed effect model will be reported, otherwise the random effect model will be reported if statistical heterogeneity exists.

Heterogeneity was explored using the chi-squared test, to provide an indication for between-study heterogeneity with a significance set at $P < 0.050$. The degree of heterogeneity observed in the results was quantified using the I-squared (I^2) statistics, which is presented as a percentage, with heterogeneity considered not to be present within a range of 0–50%. On finding significant heterogeneity in the result, a careful review of the studies will be conducted to identify the reason for this.

A funnel plot of the primary outcome was determined to look for potential publication bias in the trials (Figure 3). Data analysis was based on the results obtained according to the "intention-to-treat" principle in each original study, using the fixed or random effects model for meta-analysis.

3. Results

3.1. Results of the literature search

A total of 884 articles were identified through searches of electronic journal databases, with no additional article identified through hand searches of references of published articles. Following exclusions of duplicates, 843 articles were screened by the investigative team. Abstracts of screened papers were retrieved and a total of 11 full text articles were obtained. The texts were further screened and only seven [21–27] articles meet the inclusion criteria of the present review comparing laparoscopic single stage treatment to endoscopic two-stage treatment of common bile duct and gall bladder stones. A total of 746 patients randomised between LC and LCBDE versus ERCP/ES and LC. Figure 1 shows the flow chart for selection of articles according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis. A summary of RCT of included studies with summary results of the outcomes are shown in Table 1.

3.2. Description of included trials

Distribution of patients between either treatment arms is fairly even with 366 patients in the laparoscopic and 380 in the endoscopic treatment arms. Five trials [22–25, 27] compared LCBDE versus pre-operative ERCP + LC, while two trials [21, 26] compared LCBDE versus LC with post-operative ERCP. Most of the endoscopic two-stage treatment performed the LC during same admission, except one trial [27] that performed LC 4–6 weeks post ERCP. Follow up duration was mentioned in two trials [22, 24] while a trial [26] gives some long term complications without specifying follow-up duration. Sample size calculation was explained in three trials [23, 25, 26], while it was not clear how it was done in another trial [21].

All trials were performed on fit adult population from age 18 and above with ASA grade I and II with fitness for general anaesthesia except one trial [23] that recruits elderly patients with average age of 74 years with co-morbidities and ASA grade I to III. Sex distribution is equivalent across most trials. Only two

trials [25, 26] are multi-institutional, while the remaining a single institution. Three trials had confirmed CBD stones before randomization, one trial [27] was by MRCP/EUS, while the remaining two trials [21, 24] were by intraoperative cholangiography and had intra-operative randomization. Exclusion criteria were uniform in most studies, although some trials stated the reason for exclusion. Interventions performed were explained in all the trials except some few differences, one trial [24] performed only trancystic approach, while another trial [27] performed only the choledochotomy approach. The primary outcome is given in all trials, including data for morbidity, mortality and length of hospital stay. Duration of procedure is only reported in four trials, while total cost of hospitalisation was reported by one trial [24].

3.3. Quality assessment of included studies

The quality assessment of included studies is summarized in Table 2. Three of the trials show low risk of bias in the parameters while the remaining has low risk in two parameters. The performance and detection bias were of high risk as there was no attempt of blinding in any trials though the outcomes are objectively measured but the impact on the results and trials quality may be difficult to predict.

3.4. Effects of interventions

Primary outcome: successful ductal clearance

A total of 746 patients were randomized, 366 in the laparoscopic treatment and 380 in the endoscopic treatment arm. A total of 259 patients had successful ductal stones clearance against 254 patients in the endoscopic arm, giving a rate of 70.8% and 66.8% respectively, on an intention-to-treat basis. Our meta-analysis found no statistical difference between the treatment arms as shown in the forest plot with OR of 1.23 95% CI 0.55 to 2.75, p=0.61 and I^2 =71% using the random effects model due to statistical heterogeneity (Figure 2). The funnel plot for the studies in relation to the primary outcome on Figure 3 shows that only two out of the seven trials are outside the triangle thus indicating a lack of or at least a very low degree of publications bias.

Morbidity

The total morbidity rate was 20.2% in the laparoscopic arm and 16.6% in the endoscopic treatment, relative risk 1.23, 95% CI 0.92 to 1.66, P=0.17 and I^2=0%, using the fixed effect model. The forest plot on Figure 4 shows no statistical difference between the treatment arms.

Mortality

There were two deaths in the laparoscopic treatment and four in the endoscopic treatment arms, with no statistically significant difference between them. Risk difference of -0.0 and 95% CI -0.02, 0.01 and the forest plot using fixed effect model due to lack of heterogeneity are shown on Figure 5.

Length of hospital stay

All the trials reported the total length of hospital stay in median and range and the meta-analysis was performed by converting these data to mean and SD values. The results show no statistical difference between treatment arms with mean difference of -0.29, CI of -1.68–1.10 and P = 0.68 with a random effects model (Figure 6). One of the trials has provided inadequate data but the contact with the author for missing data by e-mail has not returned any additional information.

It is important to note that five of the studies show a shorter length of hospital stay in the single-stage laparoscopic treatment arm and the difference ranges between one and three days with statistical significance in two of the trials [21, 25], with a significant difference also between the trancystic approach to the endoscopic treatment in one study [22]. Though, one of the trials [26] is not included in the meta-analysis due to incomplete reporting, there is a low probability of tipping the overall result in favour of the single-stage treatment if this study had been included. Only one trial shows a shorter stay with endoscopic treatment [23] while one trial shows no differences in length of stay [27].

Duration of procedure

Only four trials reported on duration of procedure, data were presented in median and range, except in the study by Rogers et al. [24] that reported mean and SD. The meta-analysis was done with only three trials due to inadequate data in the fourth trial, though an e-mail request was sent to the author for the missing outcome data.

The results from the meta-analysis (Figure 7) show a statistical significance in favour of the single stage laparoscopic treatment as shorter in duration of procedure compared to the two-stage endoscopic treatment with P < 0.00001, CI -9.59 to -4.07. It is also important to note that, overall, only three of the trials reported a shorter duration of procedure in the single-stage treatment (median values) and the differences range from 15 to 18 min, with no statistical significance. Only one trial [26] reported a longer duration in the two-stage treatment arm but it was not included in the meta-analysis due to inadequate data.

Health economics

Only the study by Rogers et al. [24] reported the total hospital charges with a median of $24,399 (range 11,190–60,138) in the single stage treatment to $26,656 (range 4,496–85,085) in the two stages endoscopic treatment. The study found, however, a statistically significant difference in the professional fees between

the single stage treatment with mean (SD) of $5054 (1637) against two stage treatment with a mean of $6191(1583) (P = 0.001).

4. Discussion

This systematic review and meta-analysis of randomized controlled trials include seven studies containing 746 patients into either laparoscopic single stage treatment or to endoscopic two-stage treatment arm. The results demonstrate equivalent success in common bile duct stone clearance rate, morbidity, mortality and length of hospital stay, but a statistically significant difference in favour of the single stage technique in terms of duration of procedure. The first review on this subject by Tranter et al. [28] in 2002 involved two randomized controlled trials (RCTs) and reported similar clearance rates and length of stay between laparoscopic surgery and endoscopic treatment, but higher morbidity and mortality in the endoscopic treatment. In addition, Martin et al. [29] in a Cochrane review with 591 patients in five RCTs found no significant difference in mortality, morbidity, treatment success and procedure time. Length of stay was reported shorter in three trials but not subjected to analysis. Clayton et al. [30] found similar outcomes in the combined endoscopic and laparoscopic treatment. A recent review by Alexakis et al. [31] though currently in abstract form, suggests equivalent outcomes between single stage and two-stage management of CBD stones.

Various treatment algorithms have been developed regarding the management of gallstones with associated CBD stones [32]. It is pertinent to note that choledocholithiasis could be discovered before, during or after cholecystectomy. Our review on an intention-to-treat basis shows clearance rate of 71% in the laparoscopic treatment group compared to 69% in the endoscopic treatment cohort. On further analysis according to the actual rate of stone clearance, there is improvement in clearance rates of 87.5% to 86% between the laparoscopic to endoscopic treatment respectively. This compares favourably with various consecutive series of efficacy in the treatment of CBD stones that report bile duct clearance rates in the laparoscopic single treatment ranging from 85% to 95% and 87% to 97% in the endoscopic group [5, 6]. Interestingly, only one study in our review shows a statistical significance of laparoscopic clearance over the endoscopic clearance [23].

The endoscopic management of choledocholithiasis has a relatively low failure rate, however it has the advantage that it can be repeated multiple times and requires only sedation rather than general anaesthesia. Also delaying stone clearance should not delay gall bladder surgery as a stent could be utilised in the short-term period. This is supported by a RCT by Chang et al. [33] which demonstrated no superior outcome in pre- versus post-operative endoscopic management of choledocholithiasis.

Mortality in either treatment arms is less than 1%, which is consistent with the literature and also with previous reviews. Our review shows a morbidity rate of 20% to 16.5% in the laparoscopic and endoscopic treatment respectively. Since the LCBDE was first reported in early 90's, long term reviews of this procedure have now been reported. Waage et al. [34] conducted a long term review of 152 patients over a period of 6–72 months and also, a review by Andrew et al. [35] of 116 patients over 63 months, both demonstrate no long term biliary tract complications apart from small recurrence of CBD stones. This is similar to a study by Tranter et al. that reviewed medium to long term complications of ERCP/ES and reported recurrent CBD stone rate of 2–16%, cholangitis 1–6%, and potential risk of biliary tract cancer due to destruction of the sphincter of Oddi [28].

Cost is an important variable in health care decision making processes, and only one study compared cost between the two treatment strategies. This study reported a statistical significance in favour of the single stage treatment in regard to professional fees. Some observational studies have evaluated this variable in determining the optimum modality of treatment. Topal et al. [36] reported a consecutive series of 53 cases and demonstrated a reduction in favour of hospital cost for single stage treatment. Other studies examining healthcare costs have used different methodologies to analyse this parameter, and the conclusions are mixed [37–39]. Some important factors affecting hospital cost are; length of hospital stay, cost of operating theatre and professional fees. In this review there was no statistical difference in length of hospital stay, however two studies reported a statistical significance in this variable of between 2–3 days difference.

A limitation of this meta-analysis is that it included mostly patients who were low anaesthetic risk with ASA grades I and II, and an age range of 18–89 years. The exception is the study by Noble et al. [23] that specifically examined higher risk patients (elderly patients with co-morbidities and ASA grade I–III). Therefore a limitation of this study is that the findings may not be applicable to elderly patients with significant competing medical co-morbidities presenting with choledocholithiasis.

Further limitations of this meta-analysis are that none of the studies address the issue of performance and detection bias, but since the outcomes in the review are objectively measured, its impact on the intervention effects maybe relative. Though sample size calculation was done in three studies, this review by pooling together data has increased the power of previous published research where a clear conclusion was not possible. The population of patients in this review is still small for a common disease that affects millions of

people. The qualities of the continuous variable data are mostly non-parametric and our calculations to parametric data may be prone to errors and may affect the meta-analysis.

In conclusion, this meta-analysis demonstrates an equivalent comparison between laparoscopic and endoscopic treatment of common bile duct stones in terms of bile duct clearance rates, morbidity, mortality and length of hospital stay, but a difference in duration of the procedure. These results should be helpful to appropriately inform patients regarding the risks, benefits and alternative treatment strategies of this clinical entity.

Figure 1. Number of articles identified and screened in the systematic review.

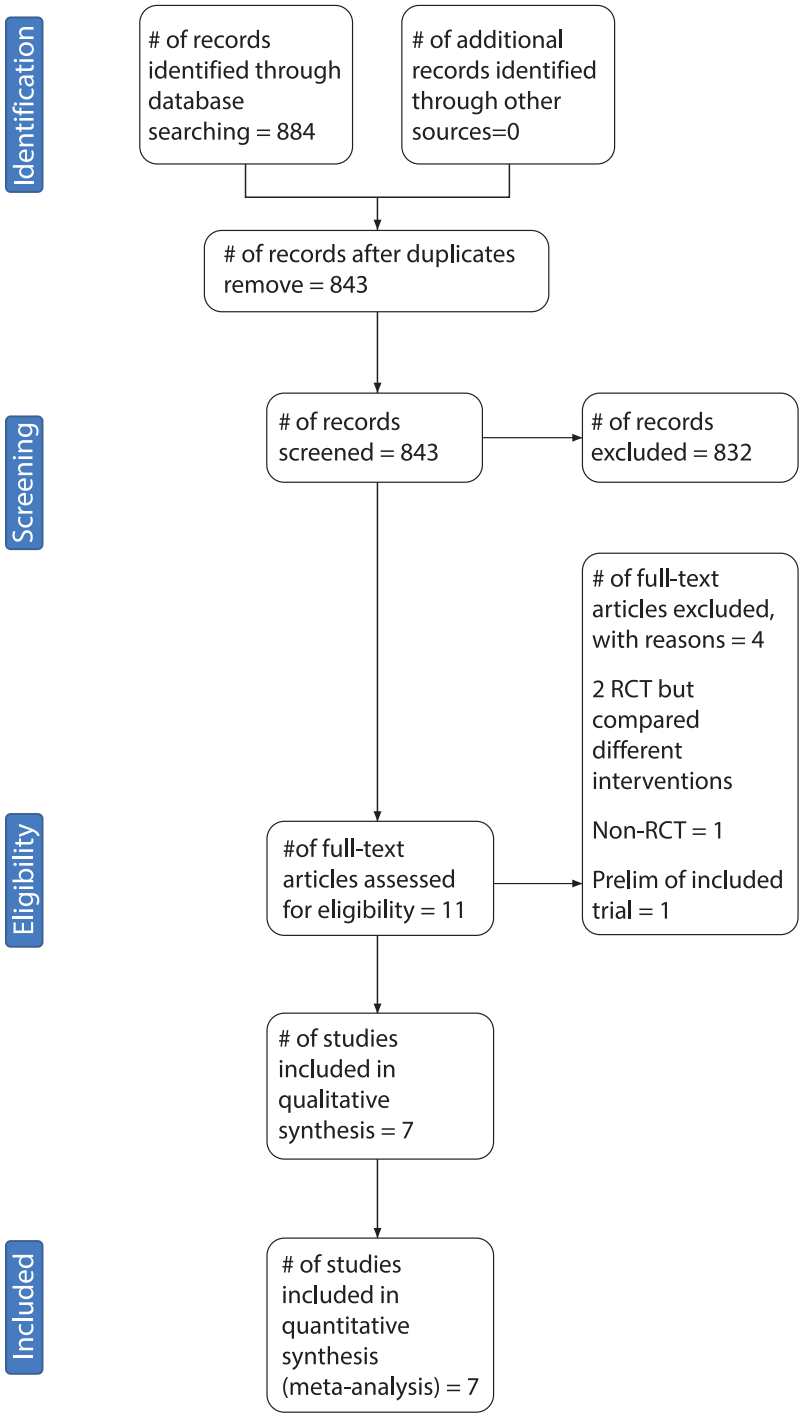

Figure 2. Forest plot of odds ratio of successful ductal stones clearance in LC + LCBDE vs ERCP/ES + LC.

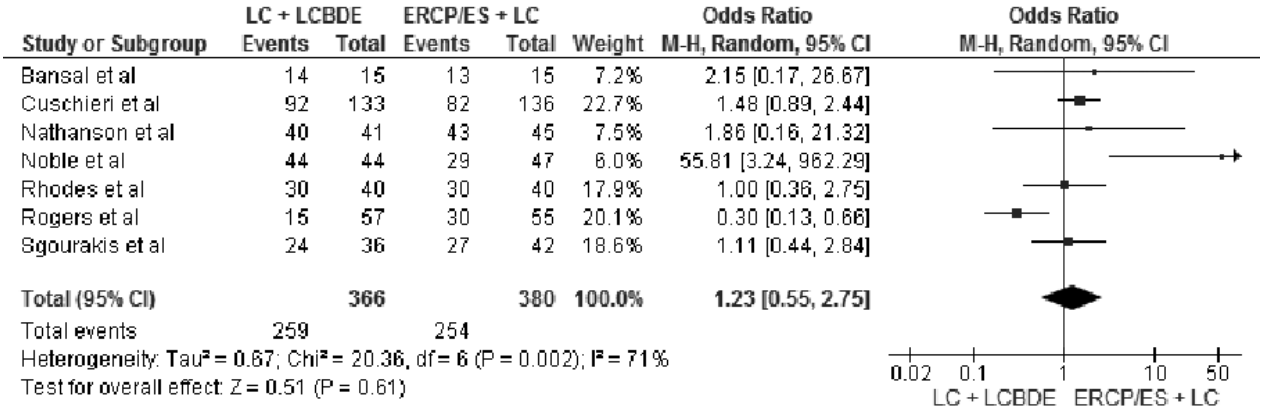

Figure 3. Funnel plot, illustrating the lack of publication bias.

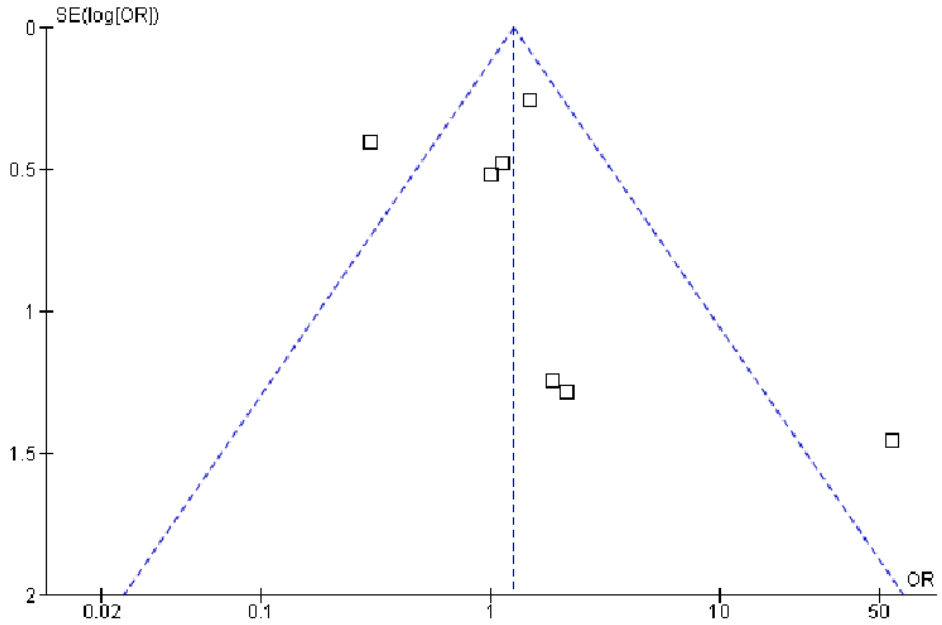

Figure 4. Forest plot of total post-operative morbidity b/w LC + LCBDE versus ERCP/ES + LC.

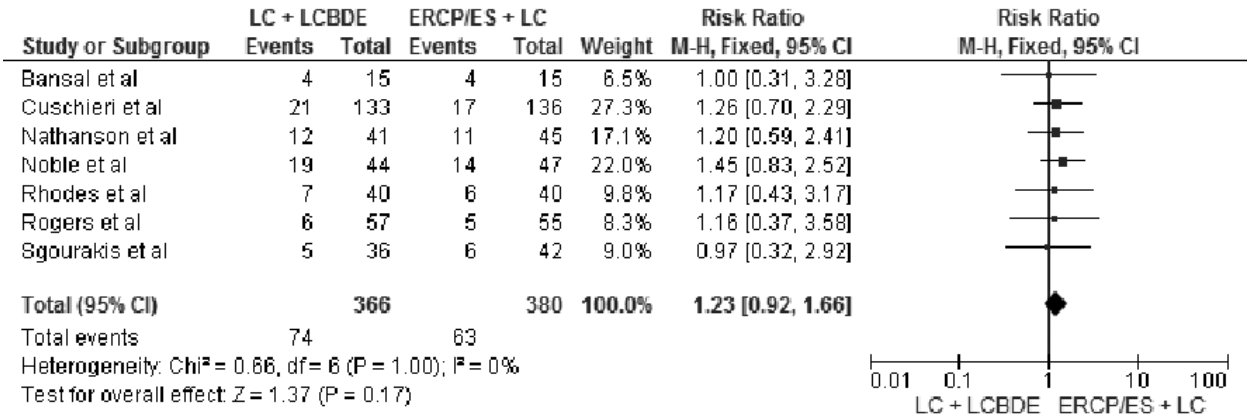

Figure 5. Forest plot of post-operative mortality b/w LC + LCBDE Versus ERCP/ES + LC.

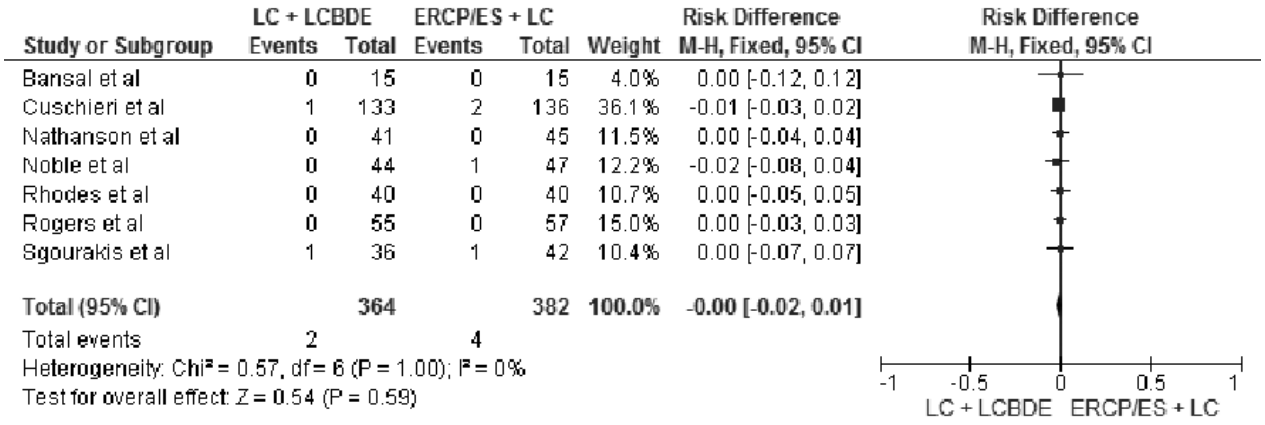

Figure 6. Forest plot of the length of hospital stay b/w LC + LCBDE Versus ERCP/ES +LC.

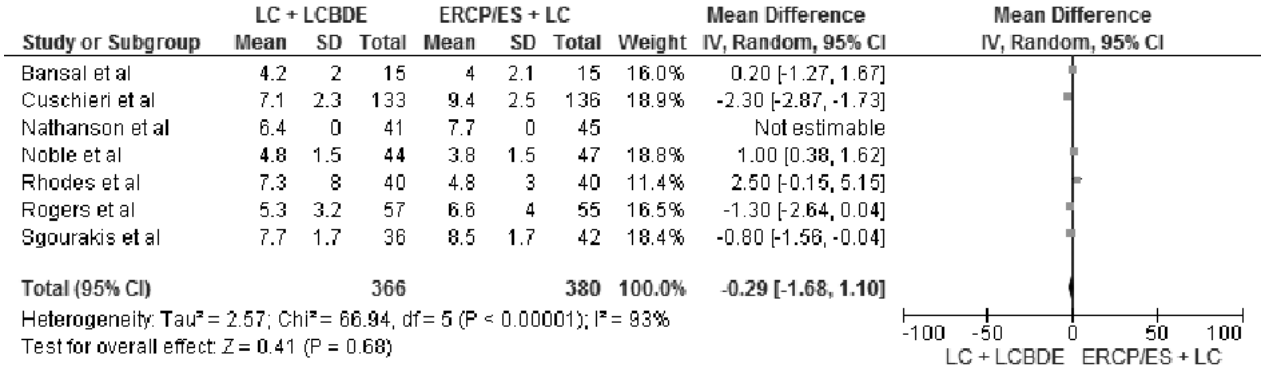

Figure 7. Forest plot of the duration of procedure b/w LC + LCBDE Versus ERCP/ES + LC.

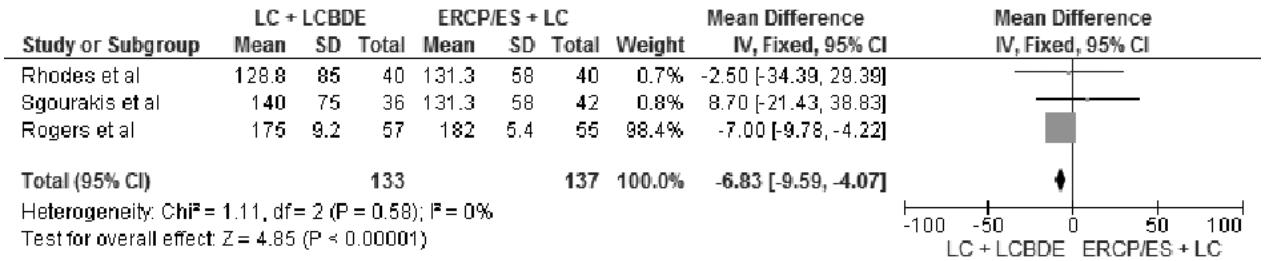

Table 1. Summary of randomized trials comparing laparoscopic against endoscopic clearance of common bile duct stones.

First author, Year of publication	***Treatment***	Number of participant s	***Age (years)***	***Gender M:F***	Successful ductal clearance n (%)	Post- operative morbidity	Post- operative mortality	Length of hospital stay (days)	Duration of procedure (mins)
Bansal 2010	Laparoscopic	15	47.1	4:11	14	4	0	4.2[a]	n/a
	Endoscopic	15	39.1	5:10	13	4	0	4[a]	n/a
Rogers 2010	Laparoscopic	57	39.9	17:40	15	6	0	4	160
	Endoscopic	55	44.6	16:39	30	5	0	5	178
Noble 2009	Laparoscopic	44	75.9	16:28	44	19	0	5	n/a
	Endoscopic	47	74.3	22:25	26	14	1	3	n/a
Nathanson 2005	Laparoscopic	41	56.1	16:25	40	12	0	6.4	158.8
	Endoscopic	45	59.6	17:28	43	11	0	7.7	147.9
Sgourakis 2002	Laparoscopic	36	43-88	15:21	24	5	1	7.4	90
	Endoscopic	42	46-89	17:25	27	6	1	9	105
Cuschieri 1999	Laparoscopic	133	19-88	6:9	92	21	1	6	n/a
	Endoscopic	136	18-89	7:18	82	17	2	9	n/a
Rhodes 1999	Laparoscopic	40	62	12:28	30	7	0	1	90
	Endoscopic	40	68	14:26	30	6	0	3.5	105
Total	Laparoscopic	366			259(70.8%)	74	2		
	Endoscopic	380			254(66.8%)	63	4		

(a) Value in mean

Table 2. Quality check of all trials.

Reference	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Bansal et al	+	?	-	-	+	+
Cuschieri et la	+	+	-	-	?	+
Nathanson et al	+	+	-	-	+	?
Noble et al	+	?	-	-	?	+
Rhodes et al	?	-	-	-	+	+
Rogers et al	?	+	-	-	?	+
Sgourakis et al	?	-	-	-	+	+

Note: (?) Unclear risk of bias; (-) high risk of bias; (+) low risk of bias.

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