

Management Cholestasis Due to Choledocal Lithiasis

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ABSTRACT

Background: The management of common bile duct stones still remains an area of controversy. Over the years, numerous authors have proposed various solutions: based on the time of cholecystectomy treatment can be preoperatively or intra and post-operative (in single-stage and two-stage).

Methods: We have selected and compared several studies that make a compare between one-stage management [Laparoscopic Cholecystectomy (LC) Plus Laparoscopic Common Bile Duct Exploration (LCBDE) or Intra-Operative ERCP] and two-stage management [laparoscopic cholecystectomy preceded or followed by Endoscopic Retrograde Cholangio Pancreatography (ERCP)] in secondary choledocholithiasis, adding our personal experience in two stage management of CBDS.

Results: In accordance with relevant randomized trials, we can say that the clinical outcome after one-stage laparoscopic/endoscopic management of bile duct stones is no different to the outcome after two-stage management.

Conclusion: Our evaluations indicate that the best treatment of choice for any patient with CBDS must be based on locally available expertise, experience of the multidisciplinary team and standardization of the technique (endoscopic, laparoscopic and surgical), as determined by success rates, rates of morbidity and mortality, costs, and patient preference.

Keywords: Common bile duct stones; Intraoperative cholangiography; Magnetic resonance cholangiography; gallstones; Endoscopic retrograde cholangioscopy; Laparoscopic cholecystectomy

INTRODUCTION

The incidence of gallstones is rather high and is referred as approximately 5%-22% among the western population [1]. Epidemiologic and clinical studies have reported that cholesterol gallstones occur infrequently in childhood and adolescence, and the prevalence of cholesterol gallstones increases linearly with age in both genders and approaches 50% at age 70 in women [2,3]. Most of the people with gallstones are asymptomatic and often they are absolutely unaware of their presence, it is even referred that no more than 15-20% of them has the probability of suffering from a biliary colic later on [4], which, once occurred, could recur more easily causing sometime serious complications, such as pancreatitis by stone's migration and biliary obstruction, that over a 10-year period can be expected to occur in 2-3% of patients with initially silent gallbladder stones [5]. Common Bile Duct Stones (CBDS) occurs in 15% of patients with cholelithiasis, 5-10% of patients undergoing laparoscopic cholecystectomy for symptomatic cholelithiasis and up to 33% of patients with acute biliary pancreatitis [6-9]. In Western countries CBDS typically originate in the gallbladder and migrate. Such secondary stones should be differentiated from primary CBDS that develop de novo in the biliary system. Primary stones are more common in south-east Asian populations, have a different composition to secondary stones, and may be a consequence of biliary infection and stasis [10,11]. The quoted prevalence of CBDS in patients with symptomatic gallstones varies, but probably lies between 10 and 20% [12-16]. However, in non-jaundiced patients with normal ducts on trans-abdominal ultrasound the prevalence of CBDS at the time of cholecystectomy is unlikely to exceed 5% [17]. Compared to stones in the gallbladder the natural history of secondary CBDS is not well understood. Whilst Collins et al. [17] have suggested that a third of patients with CBDS at the time of cholecystectomy pass their stones spontaneously within 6 weeks of surgery, it is not known with what frequency stones enter the common bile duct, or why some stones pass silently into the duodenum and others do not. What is clear is that when ductal stones do become symptomatic the consequences are often serious and can include pain, partial or complete biliary obstruction, cholangitis, hepatic abscesses or pancreatitis. Chronic obstruction may also cause secondary biliary cirrhosis and portal hypertension. Patients suspected of having CBDS are diagnosed with a combination of laboratory tests and imaging studies [18]. In 2010, the American Society for Gastrointestinal Endoscopy (ASGE) presented guidelines for the management of patients with suspected CBDS.

Based on clinical, laboratory and ultrasound 'predictors', they suggested a scheme to stratify patients into low, intermediate and high risk for choledocholithiasis [19]. The initial evaluation of suspected CBDS should include serum liver biochemical tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin) that generally increase with the duration and severity of biliary obstruction [20,21]. Transabdominal Ultrasonography (TUS) has a relatively poor sensitivity (22%-55%) for detecting CBDS [22-25]. However, TUS more reliably detects dilation of the Common Bile Duct (CBD) (sensitivity 77%-87%), a finding often associated with choledocholithiasis [26-29]. The new diagnostic techniques as Magnetic Resonance Cholangiography (MRC) and Endoscopic Ultrasound (EUS), give the opportunity to visualize the biliary tree without any invasive exploration of the ducts and share the same idea as the minimally invasive laparoscopic surgical approach. They are progressively evolving as well as the standard of care for the management of common bile duct stones, historically performed via laparotomy, which over the past decade-and-a-half has changed from open cholecystectomy with common bile duct exploration through Intraoperative Cholangiography (IOC) or choledocopy, to the routine availability of Endoscopic Retrograde Cholangioscopy (ERC) with Endoscopic Sphincterotomy (ES) for CBDS stone extraction performed before or after surgery, open in the past and laparoscopic from almost fifteen years [30]. Magnetic Resonance Cholangiography (MRC) has 85% to 92% sensitivity and 93% to 97% specificity for choledocholithiasis detection, as assessed in 2 recent systematic reviews [31,32]. However, the sensitivity of MRC seems to diminish in the setting of small (<6 mm) stones and has been reported as 33% to 71% in this clinical subset [33-35]. Computed Tomography (CT) scan is a second line exam. Conventional CT has historically demonstrated better sensitivity for choledocholithiasis than TUS in the presence of indirect signs (ductal dilation), although direct visualization of stones has not exceeded 75% [36]. Helical CT has shown improved performance over conventional CT for CBDS, with 65% to 88% sensitivity and 73% to 97% specificity [37-40]. Expense and radiation exposure have limited the use of CT as a first-line diagnostic test for choledocholithiasis. EUS give good images of the bile duct and bile duct stones with series reporting a sensitivity of 93% to 97% [41,42]. Two meta-analyses, each composed of more than 25 trials and more than 2500 patients, reported an 89% to 94% sensitivity and 94% to 95% specificity of EUS for detecting choledocholithiasis, with ERC, IOC, or surgical exploration used as criterion standards [43,44]. EUS remains highly sensitive for stones smaller than 5 mm, and its performance does not seem adversely affected by decreasing stone size [45-47]. ERC has traditionally served as a criterion standard for choledocholithiasis detection. The sensitivity of ERC with Cholangiography alone has been reported as 89% to 93% with a specificity of 100% in studies that used subsequent biliary sphincterotomy and duct sweeping with balloons/baskets as the criterion standard [48,49]. The risks of ERC include pancreatitis (1.3%-6.7%), infection (0.6%-5.0%), hemorrhage (0.3%-2.0%), and perforation (0.1%-1.1%) in prospective series of unselected patients [50-56]. Considering that the risk of adverse events is higher with ERC than with noninvasive biliary imaging studies or EUS, the use

of ERC as a diagnostic modality is best suited for those patients at high risk of CBDS because they are most likely to benefit from the therapeutic capability of ERC. The management of CBDS still remains an area of controversy. Over the years, numerous authors have proposed various solutions: based on the time of cholecystectomy treatment can be preoperatively or intra and post-operative (in single-stage and two-stage). Following the ASGE guidelines [19] the Low risk patients for choledocholithiasis with symptomatic cholelithiasis should undergo cholecystectomy however routine Intraoperative Cholangiography (IOC) or Laparoscopic Ultrasonography (LUS) should be performed at laparoscopic cholecystectomy, for purposes of both defining the biliary anatomy and for screening for CBDS. The patients with Intermediate risk may benefit from additional biliary imaging. These options include endoscopic ultrasound, magnetic resonance cholangiography, preoperative ERC, and IOC or LUS to facilitate either removal at surgery or postoperative ERC. Patients at high probability of CBDS require further evaluation of the bile duct; because of the frequent need for therapy, typically preoperative ERC or operative cholangiography are undertaken. Two randomized, controlled trials compared 2-stage management (preoperative ERC followed by laparoscopic cholecystectomy) with an all-surgical approach of laparoscopic IOC and transcystic stone removal or laparoscopic choledochotomy for patients at high risk of choledocholithiasis [57,58]. In these studies, there was no difference in morbidity, mortality, or primary ductal clearance rates (88%) between the 2 arms. Other potential options include intraoperative or postoperative ERC for patients with positive IOC findings; laparoscopic ante grade placement of a transpapillary stent to ensure biliary access at postoperative ERC may also be considered [59]. We have selected and compared several studies that make a compare between one-stage management [laparoscopic cholecystectomy (LC) plus laparoscopic common bile duct exploration (LCBDE) or intra-operative ERC) and two-stage management [laparoscopic cholecystectomy preceded or followed by endoscopic Retrograde Cholangio Pancreatography], adding our personal experience in two stage management of CBDS.

MATERIALS AND METHODS

Relevant studies were identified by searching databases, lists of articles and communication with experts. The electronic search was applied to Medline/PubMed from 1990 to 2011 for records in English. We used following search items: common bile duct stones/-calculi; bile duct stones/calculi; ERCP; endoscopic sphincterotomy; and laparoscopic ductal clearance/choledochotomy/bile duct exploration. A meta-analysis was performed using Statistica8.0 by Stat Soft 1984-2007. For dichotomous variables, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Fixed-effect and random effects models (owing to a number of small studies) were used. In case of discrepancy between the two models, the random effects results are reported; otherwise only the results of the fixed-effect model are reported. The level of significance was set at $P < 0.050$. Our personal experience covers a period from September 1997 to December 2014 a total of 1550 patients with biliary lithiasis was treated in our department. The clinical presentation and diagnosis was different: 931 stones of gallbladder, 463 acute

biliary pancreatitis and 156 with CBDS without pancreatic implication. Preoperative diagnosis was based on a combination of clinical assessment (biliary colics with or without jaundice), laboratory tests (such as aspartate amino-transferase, alanine amino-transferase, gamma-glutamyltranspeptidase, alkaline phosphatase, total and conjugated bilirubin, pancreatic amylase and lypase) and instrumental investigations including abdominal Ultrasound (US), computer tomography and magnetic resonance cholangiography. The diagnostic instrumental iter was modified during the years because in the period between 1997-2002 the diagnosis was based on ultrasound and computer tomography while in the next period (2003-2014) magnetic resonance cholangiography was performed. In this study we examined 156 patients with CBDS without pancreatic implication. The male/female ratio was 57/99, with a median age 63 years (range: 32-84). In 119 patients (76%) the diagnosis was defined preoperatively, in the remaining 37 (24%) the CBDS was suspected by increased cholestasis, dilated CBD greater than 8 mm and biliary colics presenting with jaundice. We treated 138 patients (88.46%) with CBDS with preoperative ERC and endoscopic sphincterotomy. This procedure allowed us to diagnose and remove the stones respectively in 100% (138/138) and 88.41% (122/138) of cases. 18 of 156 patients (11.54%) were not eligible to endoscopic approach. LC was performed in 122 patients (78.20%) while in 21.80% (34/156) was treated with open cholecystectomy and choledocholithotomy, all data are shown in Figure 1. In the open surgery, after exploration of CBD a latex T-tube was placed through the choledochotomy site and the removal after check cholangiography was performed after a minimum of 3 months. The bioumoral and instrumental data were subjected to univariate and multivariate analysis using Fisher exact test. A p-value of 0.05 or less was considered statistically significant. The 6 and 12 months follow-ups for 115 patients included blood and instrumental tests with clinical observation.

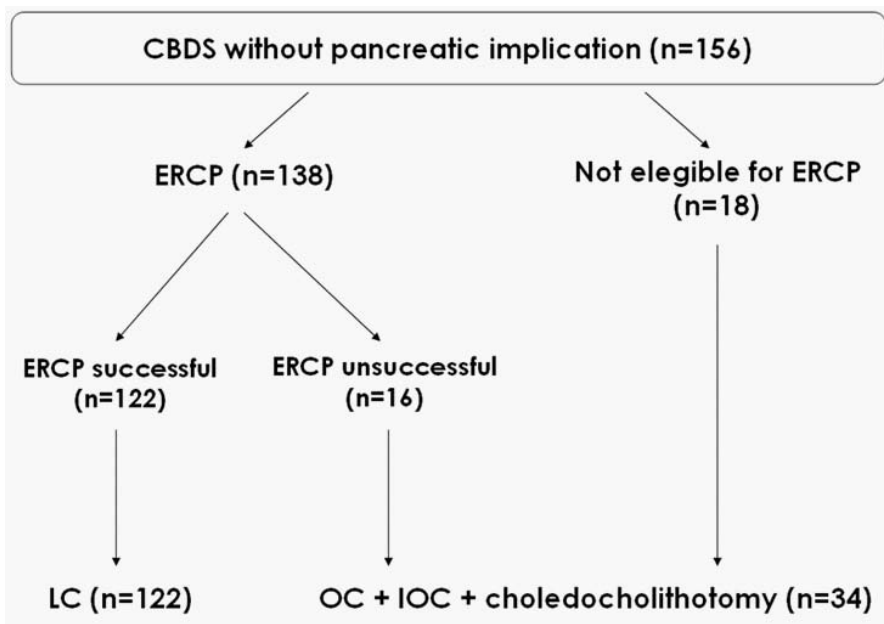


Figure 1: Treatment of CBDS without pancreatic implication in 156 patients.

RESULTS

We selected nine studies, of which four studies compared ERC followed by LC against laparoscopic CBD surgery [57,63-65], two studies compared LC followed by ERC against laparoscopic CBD surgery [60,61] and two studies compared ERC+LC against LC plus intra-operative ERC [62,66]. Outcomes for 933 patients [462 (49.5%) in the one-stage management and 471 (50.5%) in the two-stage management group] were examined (Table 1). Successful duct clearance was achieved in 342/471 (72.6%) of patients in the two-stage group and in 344/462 (74.4%) in the one-stage management group. No significant difference between the two groups was observed [OR (fixed) = 0.89 (95% CI = 0.65–1.21), P = 0.46]. Mortality was 4/471 (0.8%) in the two-stage management group and 3/462 (0.6%) in the one-stage management group. No significant difference between the two groups was observed [OR (fixed) = 1.2 (95% CI = 0.32–4.52), P = 0.79]. Total patient morbidity was 76/471 (16.1%) in the two-stage group and 92/462 (19.9%) in the one-stage group. No significant difference between the two groups was observed [OR (fixed) = 0.75 (95% CI = 0.53–1.06), P = 0.10]. Major patient morbidity was 39/471 (8.3%) in the two-stage group and 40/462 (8.6%) in the one-stage group. No significant difference between the two groups was observed [OR (fixed) = 0.95 (95% CI = 0.60–1.52), P = 0.84]. Additional procedures were required in 76/471 (16.1%) in the two-stage group and in 42/462 (9%) in the one-stage management group. No significant difference between the two groups was observed [OR (random) = 1.58 (95% CI = 0.76–3.30), P = 0.22]. In our experience with two-stage management. After preoperative exams, 138 patients (88.46%) were subjected to ERC. During the diagnostic phase the CBDS was always demonstrated (138/138 – 100%). The cleaning of CBD was performed though the ES followed by CBDS extraction by Dormia Basket or endoscopic papillary balloon dilatation without ES. In our experience the success rate was 88.40% (122/138). 11.60% (16/138) of the ERC wasn't successful and 18 of 156 patients (11.54%) were not eligible to endoscopic approach due to location and size of the stones. All these were summarized in (Table 2). Mean operative time for LC was 45 min ± 20 and the laparoscopic technique was performed with antegrade approach. After surgery there were 9 cases (7.38%) of umbilical port-site infection treated with medical therapy and 3 umbilical hernias (2.46%). Regarding the complications related to ERC/ES, the major morbidity were 2 duodenal perforations (1.64%): the first patient was submitted to derivative surgical procedure, the second one was treated only with conservative medical therapy. Other complications were 3 severe acute pancreatitis and 2 hemobilia, treated with medical approach. In our experience we have observed no case of cholangitis. Among minor morbidity there was only 8.20% of mild acute pancreatitis (10/122) uncovered with the increase of pancreatic enzymes and characterized by a spontaneous resolution. All ERC complications with its Clavien-Dindo [67] grade are shown in (Table 3). After 6 and 12 months we have reevaluated 115 patients who had undergone ERC/ES (94.26%). They were subjected to clinical exam, blood tests and abdominal US. 6 months follow-up only 3 patients (2.61%) reported yet symptoms related to a probable obstacle to the biliopancreatic outflow. Symptomatology was characterized

by a pain like “biliary colic” (localized to the right hypochondrium and epigastrium sometimes radiated to the back). Laboratory tests showed mild elevation of markers of cholestasis, while performing an abdominal ultrasound there was no dilation of CBD. We related these outcomes to the evolution of the scar after ES, indeed the most common case was an inflammatory stenosis of Oddi’s sphincter. The treatment was only medical. The subsequent follow-up to 12 months was negative for all the patients. In conclusion, in accordance with relevant randomized trials, we can say that the clinical outcome after one-stage laparoscopic/endoscopic management of bile duct stones is no different to the outcome after two-stage management. These results indicate that the best treatment of choice for any patient with CBDS must be based on locally available expertise, experience of the multidisciplinary team and standardization of the technique (endoscopic, laparoscopic and surgical), as determined by success rates, rates of morbidity and mortality, costs, and patient preference.

Table 1: Summary of randomized trials comparing two-stage (endoscopic common duct clearance and laparoscopic cholecystectomy) vs. one-stage (laparoscopic surgery alone or combined with intra-operative endoscopy).

Study	Author	Year	Treatment	n	Duct clearance successful	Mortality	Morbidity (Total)	Morbidity (Major)	Additional procedures required	Length of stay (median, days)
1	Rhodes [60]	1998	LC+ERCLC+LCBDE	40	37	0	6	4	10	3.5
				40	30	0	7	2	10	1
2	Cuschieri [57]	1999	ERC+LC	133	82	2	17	9	17	9
			LC+LCBDE	133	92	1	21	9	17	6
3	Sgourakis [58]	2002	ERC+LC	42	27	1	6	3	5	9
			LC+LCBDE	36	24	1	5	2	4	7.4
4	Nathanson[61]	2005	LC+ERC	45	43	0	11	6	3	7.7
			LC+LCBDE	41	40	0	12	7	3	6.4
5	Morino [62]	2006	ERC+LC	45	36	0	4	2	15	8
			LC+ i.o.ERC	46	44	0	5	4	2	4.3
6	Noble [63]	2009	ERC+LC	47	29	1	16	8	18	3
			LC+LCBDE	44	38	0	23	8	0	5
7	Rogers [64]	2010	ERC+LC	55	30	0	5	0	1	5
			LC+LCBDE	57	15	0	6	0	2	4
8	Bansal [65]	2010	ERC+LC	15	13	0	5	2	2	4
			LC+LCBDE	15	14	0	6	2	1	4.2
9	Tzovaras [66]	2011	ERC+LC	49	45	0	6	5	5	5.5
			LC+ i.o.ERC	50	47	1	7	6	3	4
Totals										
			Two stage (endoscopy followed by Surgery)	471	342 (72.6%)	4 (0.8%)	76 (16.1%)	39 (8.3%)	76 (16.1%)	
			One stage (LCBDE or intra-operative endoscopy)	462	344 (74.4%)	3 (0.6%)	92 (19.9%)	40 (8.6%)	42 (9%)	

Table 2: Clinical outcome after two-stage treatment.

Preoperative diagnosis N (%)	156/156 (100%)
Success rate (ERCP) N (%)	122/138 (88.40%)
LC operative time Mean \pm SD	45 min \pm 20
Hospital stay (ERCP + LC) Mean	9 days
Resumption of alimentation Mean	4 days
Umbilical port-site infection N (%)	9/122 (7.38%) (Clavien-Dindo grade I-d)
Umbilical hernias N (%)	3/122 (2.46%)

ERCP: Endoscopic Retrograde Cholangio Pancreatography; LC: Laparoscopic Cholecystectomy;
SD: Standard Deviation

Table 3: ERPC complication.

Complications	N (%)	Clavien-Dindo grade
Major morbidity		
Duodenal perforation	2/122 (1.64%)	I case - III-b II case - II
Severe acute pancreatitis	3/122 (2.46%)	II
Hemobilia	2/122 (1.64%)	III-a
Cholangitis	---	---
Minor morbidity		
Mild acute pancreatitis (hyperamylasemia)	10/122 (8.20%)	I

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