A randomized controlled trial of emergency LCBDE + LC and ERCP + LC in the treatment of choledocholithiasis with acute cholangitis

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Abstract

Introduction: *Emergency biliary drainage is the basic treatment for acute cholangitis caused by choledocholithiasis.*
Aim: *To compare the effectiveness and safety of emergency laparoscopic common bile duct exploration combined with laparoscopic cholecystectomy (LCBDE + LC) and endoscopic retrograde cholangiopancreatography combined with laparoscopic cholecystectomy (ERCP + LC) for the treatment of choledocholithiasis combined with grade I or II acute cholangitis.*
Material and methods: *A total of 80 patients were enrolled in the study, with 40 cases in each group. A prospective randomized controlled study method was adopted, and the eligible patients were randomly divided into two groups in a ratio of 1 : 1 and treated with emergency LCBDE + LC and ERCP + LC, respectively. The relevant clinical data of the two groups were compared.*
Results: *The operation duration was longer and blood loss was greater in the LCBDE + LC group than in the ERCP + LC group, but the therapeutic cost was significantly lower in the former than in the latter. The differences were statistically significant ($p < 0.05$ in all). There was no severe complication in either group. The total number of cases with complications, incidence of postoperative acute pancreatitis and incidence of hemorrhage were higher in the ERCP + LC group than in the LCBDE + LC group, while the incidence of bile leakage was lower in the former than in the latter. The differences were statistically significant ($p < 0.05$ in all).*
Conclusions: *Both protocols were safe and feasible in the management of grade I or II acute calculous cholangitis. Compared with the protocol of ERCP + LC, the protocol of LCBDE + LC had the advantages of fewer complications and lower therapeutic costs and is worthy of clinical promotion.*

Key words: *choledocholithiasis, acute cholangitis, laparoscopic common bile duct exploration, endoscopic retrograde cholangiopancreatography.*

Introduction

Acute cholangitis caused by choledocholithiasis is a common clinical abdominal disease with rapid onset that can cause systemic inflammatory response syndrome, sepsis, and even multi-organ functional impairment in severe cases. Emergency biliary drainage is the basic principle of treatment [1], but for grade I and grade II acute cholangitis, the biliary drainage should be combined with the management of bile duct stones [2]. Currently, endoscopic retrograde cholangiopancreatography combined with laparoscopic cholecystectomy (ERCP + LC) and laparoscopic common bile duct exploration combined with laparoscopic cholecystectomy (LCBDE + LC)

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are the two main minimally invasive options for the treatment of gallbladder stones combined with choledocholithiasis, each of which has advantages and disadvantages. It is believed that the combined approach to bile duct stones with selective use of ERCP followed by LC is a good therapeutic alternative. Nevertheless, the usual selection criteria for ERCP may lead to unnecessary exploration [3]. LCBDE surgery is clean and thorough, avoiding Oddi sphincterotomy. However, there is a risk of bile leakage and long-term indwelling of the T tube. As for ERCP, less trauma and better recovery could be found, but Oddi's sphincter needs to be incised and two operations are required. It appears to be necessary to confirm the suitable and effective diagnostic and therapeutic strategy.

Aim

In patients with acute cholangitis, the question of which of the two protocols is superior is controversial. In the present study, patients with grade I or grade II acute cholangitis with gallbladder stones and choledocholithiasis were adopted as the study subjects. A prospective randomized study method was used to compare the effectiveness and safety of the two therapeutic protocols, including operation success rate, operation duration, blood loss, and postoperative complications, to provide a reference for the choice of clinical treatment. Beside these primary outcomes, postoperative pain score, postoperative ventilation duration, length of hospital stay, and therapeutic cost were also considered.

Material and methods

Inclusion and exclusion criteria

The present study was a prospective randomized controlled trial. Eligible patients were divided into two groups in a ratio of 1 : 1 by a simple method of a random number table, and emergency LCBDE + LC or ERCP + LC was performed by the different groups of doctors. The inclusion criteria were as follows: (1) according to the widely adopted Tokyo guidelines for the diagnosis and treatment of acute cholangitis (TG18) [3], patients who met the diagnostic criteria for cholangitis and met the classification criteria for grade I or grade II acute cholangitis grade I (mild): acute cholangitis; grade II (moderate): acute cholangitis combined with any two of the following conditions: 1) white blood cells (WBC) count ($> 12 \times 10^9$/l, $< 4 \times 110^9$/l); 2) high fever (≥ 39°C); 3) age (≥ 75 years); 4) jaundice (TBil ≥ 85.5 μmol/l); 5) low protein ($< 0.7\times$ upper limit of normal value), together with a clear imaging diagnosis for choledocholithiasis combined with gallbladder stones; (2) patients with no atrophy, porcelain or other difficult LC manifestations; (3) patients with the diameter of the common bile duct > 8 mm, the number of common bile duct stones < 3, and the maximum diameter of the stone < 1.5 cm; and (4) patients who understood and were willing to participate in the present study and signed an informed consent form. The exclusion criteria were as follows: (1) patients with severe chronic disease or cardiopulmonary insufficiency; (2) patients with an American Society of Anesthesiologists score of III or IV who had been assessed by an anesthesiologist to be intolerant of general anesthesia; (3) patients with a previous history of abdominal surgery; and (4) patients who had a preference for a particular surgical protocol. The study started in July 2018 and ended in June 2020, and a total of 80 patients were included, with 40 cases in each group.

Therapeutic protocols

The emergency LCBDE + LC was performed by one group of physicians, and ERCP + LC was performed by another group of physicians. In the LCBDE + LC group, after the preoperative evaluation of the patient on admission, the emergency laparoscopic cholecystectomy + choledocholithotomy was performed. A T-drain was routinely placed in the common bile duct, and a laparoscopic drain was routinely placed in the small omental orifice. If there was difficulty in the laparoscopic operation, such as unclear anatomy and hemorrhage, the procedure was converted to open surgery and the experiment was terminated. In the case of a successful operation, the calculi were removed with a choledochoscope and lithotomy net. Moreover, the T-drain was clamped approximately 2 weeks post-operatively, and the cholangiogram was routinely performed 8 weeks later. If there were no residual stones, the drain was removed. If there were residual stones, the drain was removed after the stone had been removed by the trans-T-tubular sinus choledochoscopy. In the ERCP + LC group, after the preoperative evaluation of the patient on admission, the emergency ERCP was performed. For patients who met the indications for stone extraction,

an archotomy knife was used to perform the papillary sphincter dissection followed by appropriate balloon dilation, and then the stone was extracted appropriately according to the size and texture of the stone, and the diameter of the common bile duct. In the case of successful removal of the stone in the common bile duct, a nasobiliary tube was routinely placed, and observation of any complications after endoscopic therapy was conducted. If there was no complication after the endoscopic therapy, the LC was completed in 2–3 days. If complications such as pancreatitis occurred after endoscopic therapy, the LC was completed 2–3 days after the complications had been stabilized. If the stones in the common bile duct could not be removed by the endoscopic therapy, the procedure was converted to emergency LCBDE + LC and the experiment was terminated.

Observation indicators

The trial adhered to established procedures to maintain separation between staff who take outcome measurements and staff who perform the surgery. Staff members who obtained outcome measurements were not informed of the group assignment. Physicians who performed the operation did not take outcome measurements.

The success rate of surgery, operation duration, blood loss, 1-day postoperative pain score, postoperative ventilation duration, length of hospital stay, therapeutic cost, and occurrence of postoperative complications such as acute pancreatitis, residual stone, bile leakage, hemorrhage, and gastrointestinal perforation were recorded in both groups. Among these indicators, the intraoperative blood loss in the ERCP + LC group referred to the sum of the blood loss in the two surgical procedures. The 1-day postoperative pain score in the ERCP + LC group meant the 1-day postoperative pain score after emergency ERCP. The postoperative hemorrhage in the LCBDE + LC group referred to postoperative abdominal drainage of the hemorrhagic fluid, and in the ERCP group, it referred to postoperative gastrointestinal hemorrhagic symptoms such as blood vomiting, bloody stools, and large amounts of melena.

Statistical analysis

SPSS 20.0 software was adopted for the statistical analysis. The data were expressed as mean ± standard deviation. The *t*-test was adopted for the comparison of measurement data between groups, e.g. 1-day postoperative pain score, postoperative ventilation duration, length of hospital stay, operation duration, blood loss, therapeutic cost. The χ^2 test was used to compare the success rate and complications between two groups. $P < 0.05$ was considered significant.

Results

Comparison of baseline data

There were 40 cases in the LCBDE + LC group, including 17 males and 23 females. The average age was 64.9 ±13.9 years. There were 40 cases in the ERCP + LC group, including 19 males and 21 females, with an average age of 67.8 ±13.4 years. There was no serious fundamental disease in any of the patients. There was no significant difference in the levels of direct bilirubin, alanine aminotransferase, white blood cell count, or serum albumin between the two groups before surgery ($p > 0.05$ in all), as shown in Table I.

Comparison of relevant perioperative indicators

There was no significant difference in the success rate of surgery, 1-day postoperative pain score, post-

Table I. Comparison of baseline data between the two groups

Group	*N*	Age [years old]	Number of stones (*N*)	Diameter of common bile duct [mm]	White blood cell count [× 10^9]	Total bilirubin [μmol/l]	Alanine aminotransferase [U/l]
LCBDE + LC	40	64.9 ±13.9	2.1 ±0.6	12.8 ±3.6	14.9 ±4.7	85.2 ±10.9	156.67 ±30.45
ERCP + LC	40	67.8 ±13.4	1.8 ±0.7	12.1 ±4.1	15.4 ±5.3	82.4 ±12.6	165.72 ±39.37
t		1.368	1.354	0.853	2.762	3.618	4.161
P-value		0.534	0.173	0.189	0.115	0.427	0.532

Table II. Comparison of relevant peri-operative indicators between the two groups

Group	*N*	Operation duration [min]	Blood loss [ml]	Number of successful operations	Post-operative 1d VAS scores	Ventilation duration [h]	Length of hospital stay [d]	Hospitalization cost (ten thousand Yuan)
LCBDE + LC	40	125.61 ±25.6	48.6 ±15.28	39	3.76 ±0.53	40.24 ±4.37	8.76 ±1.91	2.742 ±0.650
ERCP + LC	40	79.52 ±28.1	25.12 ±7.23	38	4.17 ±0.62	39.24 ±5.71	9.59 ±3.78	3.757 ±0.604
χ^2/t		6.270	4.573	0.346	2.847	1.243	1.325	3.855
P-value		0.001	0.037	0.556	0.084	0.857	0.163	0.000

Table III. Comparison of postoperative complications between the two groups

Group	*N*	Acute pancreatitis	Residual stone	Bile leakage	Hemorrhage	Gastrointestinal perforation	Total complications
LCBDE + LC	40	0	1	5	1	0	7
ERCP + LC	40	7	3	0	6	0	16
χ^2		7.671	1.053	5.333	3.914		4.943
P-value		0.006	0.305	0.021	0.048		0.026

operative ventilation duration, or length of hospital stay between the two groups of patients ($p > 0.05$ in all). However, the operation duration was longer and blood loss was greater in the LCBDE + LC group than in the ERCP + LC group, and the therapeutic cost was significantly lower in the former group than in the latter group. The differences were statistically significant ($p < 0.05$ in all), as shown in Table II.

Occurrence of postoperative complications

There were no serious complications such as gastrointestinal perforation. Postoperative pancreatitis, hemorrhage and biliary fistula were all mild complications, which were relieved after conservative treatment. The total incidence of complications and incidence of postoperative acute pancreatitis and hemorrhage in the ERCP + LC group were significantly higher than those in the LCBDE + LC group, and the incidence of bile leakage was lower in the ERCP + LC group than in the LCBDE + LC group. The differences were statistically significant ($p < 0.05$), as shown in Table III. There were no cases of re-operation, re-hospitalization or death in the two groups.

Discussion

Cholelithiasis is a common and frequently occurring disease in general surgery. At present, the incidence of cholelithiasis in China is 10% [4]. Gallstones combined with choledocholithiasis account for 5–29% of cases of cholelithiasis, with an average of 18%. Acute cholangitis is one of the serious complications of common bile duct stones. Acute cholangitis with different severity requires different therapeutic measures. For patients with grade III acute cholangitis, biliary drainage should be performed as soon as possible under the condition of stable pulmonary and cardiovascular functions, and endoscopic sphincterotomy (EST) or surgery should be performed to remove the etiology after the vital signs have stabilized [2]. For grade I and grade II acute cholangitis, in addition to early biliary drainage, the treatment of gallstones and choledocholithiasis should be considered. Currently, ERCP + LC and LCBDE + LC are the two main minimally invasive methods for the treatment of gallbladder stones and choledocholithiasis [2, 5].

For patients with acute cholangitis, ERCP can be used to remove the stones while draining. After the infection is under control, a second-stage laparoscopic cholecystectomy can be performed. This protocol is currently the most commonly used minimally invasive treatment in clinical practice. However, ERCP requires the surgeon to have high operational skills, and there are risks of serious complications such as postoperative hemorrhage, acute pancreatitis, and

duodenal perforation. More importantly, EST of the duodenal papilla is often required for stone removal under ERCP, which destroys the structure and function of the Oddi sphincter and increases the risk of retrograde infection of the biliary tract and the long-term recurrence of stones. Consequently, a postoperative second-stage LC is required, which increases the trauma and pain of the patient [6]. However, the management of common bile duct stones in the era of laparoscopic surgery is still controversial. One study conducted to investigate the safety, feasibility, success rate and short-term results of the selective use of ERCP in patients undergoing laparoscopic cholecystectomy found that the combination of perioperative ERCP and LC could a useful approach for the management of cholelithiasis [7]. Due to the limited sample size in this study, the conclusion needs to be confirmed in future research.

With the continuous advancement in laparoscopic technology and choledochoscopy equipment, selective LCBDE has been widely developed in clinical practice. It is generally believed that LC combined with LCBDE can simultaneously treat gallstones and choledocholithiasis within one operation with a short length of hospital stay and low therapeutic costs. It also has the advantages of preserving the function of the Oddi sphincter and low incidence of long-term complications. The stone removal rate, incidence of complications at an early stage, and mortality are better than or equal to those in the EST combined with LC group [8]. However, for acute grade I or grade II acute cholangitis, there are relatively few studies that report whether emergency LCBDE + LC is safe and effective.

In the present study, there was no significant difference in the success rate of surgery or the incidence of residual stones between the emergency LCBDE + LC group and the ERCP + LC group, which was consistent with the results of elective surgery reported in the domestic and foreign literature [9, 10]. In the LCBDE + LC group, the operation was completed successfully in 39 cases, and in 1 case, the operation was converted to laparotomy due to gallbladder delta adhesion and unclear anatomy. In the ERCP + LC group, in 2 cases, it was not possible to complete the ERCP due to the existence of a huge duodenal diverticulum and difficulty in papillary intubation, and therefore the operation was converted to LCBDE + LC, which suggested that LCBDE + LC might be a good solution following the failure of ERCP. One patient in the LCBDE + LC group was found to have residual stones by the postoperative T-tube cholangiography, and the stones were successfully removed through the T-tube sinus with a choledochoscope. Three cases in the ERCP + LC group were found to have choledocholithiasis by the postoperative nasal cholangiography, and ERCP was performed again to remove the stones. However, the operation duration and blood loss in the LCBDE + LC group were higher than those in the ERCP + LC group. We believed this might be correlated with the congestion of the bile duct wall and edema in the acute inflammation phase, which increased the risk of hemorrhage and the difficulty in removing stones. According to a study, patients in ERCP + LC group had a higher common bile duct stone clearance rate and a lower postoperative bile leakage rate [11]. In this study, there was no significant difference in the 1-day postoperative pain score, and another study showed that single-stage management of patients with gallbladder and CBD stones and EST followed by laparoscopic cholecystectomy were similar in terms of improvement in quality of life [12]. Furthermore, considering the safety and effectiveness of the operation, T-tubes were placed in the patients for 8 weeks after the operation in the present study, which also increased the duration of bile duct fixation and brought pain, infection, inconvenience to life, etc., and is also a problem to be considered when doctors and patients choose treatment plans. The therapeutic costs in the ERCP + LC group significantly exceeded those in the LCBDE + LC group, and the difference between the two groups was statistically significant. When comparing the details of the cost, it is evident that the main extra cost was due to the fact that the supplies in the ERCP were more expensive. Moreover, 7 patients developed pancreatitis after ERCP, which prolonged the treatment course and increased the therapeutic cost. It was consistent with a meta-analysis showing that ERCP + LC is associated with a higher rate of pancreatitis [11], and this study also showed that patients in the ERCP + LC group had higher CBD stone clearance and less bile leakage.

According to the data concerning postoperative complications, neither group of patients had serious complications such as gastrointestinal perforation, severe pancreatitis, hemorrhage that was difficult to control by conservative treatment, or bile leakage, indicating that both surgical protocols were safe.

However, 7 patients in the LCBDE + LC group developed complications, which was significantly lower than the number in the ERCP + LC group, and the difference was statistically significant ($p < 0.05$). In the LCBDE + LC group, there were 5 patients with bile-like fluid in the drainage tube post-operatively. It was considered to be a small amount of bile leakage around the T tube wall. After ensuring the smooth drainage of the T tube and with the drainage via the abdominal drainage tube, the symptoms improved in 5–9 days. In the ERCP + LC group, 6 patients had symptoms of gastrointestinal hemorrhage such as melena, and 7 patients had acute postoperative pancreatitis. The incidence of pancreatitis was 17.5%, which was higher than the incidence rates reported in the literature [13, 14]. However, the severity of the above complications was relatively mild, and all the patients healed after treatment such as fasting and enzyme inhibition. The higher incidence of complications in this group might be due to the incarceration of the choledocholithiasis, and edema of the bile duct wall and duodenal papillary.

However, there were still limitations in this study: (1) The patients were followed up to observe short-term recovery, but for long-term efficacy, several years of follow-up were needed; (2) this was a single-center randomized controlled trial, so a multi-center study was needed to further verify the conclusions of this study.

Conclusions

The two protocols were safe and feasible in treating grade I and grade II acute calculous cholangitis. Compared with the ERCP + LC protocol, the LCBDE + LC protocol had the advantages of preserving the structure of the Oddi sphincter, fewer complications (pancreatitis, hemorrhage and bile leakage), and a lower therapeutic cost, and therefore it is worthy of clinical promotion. However, there were limitations in the present study, such as the small sample size. Whether emergency LCBDE + LC could be widely used in the treatment of acute calculous cholangitis still needs to be confirmed by clinical studies with a larger sample. Because of the complexity of acute cholangitis, it was recommended that clinicians adhere to individualized therapeutic strategies and select reasonable treatment options based on their experience, the technical level, and characteristics of the disease.

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Conflict of interest

The authors declare no conflict of interest.

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