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Surgical treatment of acute calculous cholecystitis complicated with hepatic dysfunction

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Abstract

To evaluate the timing, feasibility, and necessity of early laparoscopic cholecystectomy (LC) in the management of patients with acute calculous cholecystitis complicated with hepatic dysfunction.

The clinical data of 60 patients with acute calculous cholecystitis complicated with hepatic dysfunction treated from January 2016 to January 2018 were analyzed retrospectively. A total of 32 patients underwent LC within 72 hours of the cholecystitis attack, 28 patients after 72 hours. The results were compared with those from 28 patients with delayed LC.

All the patients were operated by experienced surgeons, and no LC transfer to open operation. No significant differences were detected in the operation time, postoperative complications, intraoperative blood loss, white TBIL, ALT, GGT before and after the operation between the 2 groups ($P > .05$). Patients who underwent early LC had a short hospital stay and fewer hospital costs ($P < .05$). All the patients were cured.

It is safe, feasible, and necessary to perform LC within 72 hours in patients with acute calculous cholecystitis complicated with hepatic dysfunction. Such patients show a high positive correlation between the inflammation of acute calculous cholecystitis and the damage of hepatic function.

Abbreviations: HE = hematoxylin-eosin, LC = laparoscopic cholecystectomy, NO = nitric oxide.

Keywords: cholecystitis, complications, gallbladder stone, hepatic dysfunction, laparoscopic cholecystectomy (LC)

1. Introduction

Gallstone with cholecystitis is the most common disease in hepatobiliary surgery and one of the most common surgical acute abdomens, showing an increased incidence of gallstone recently.[1] Impaired liver function is one of the most common complications of acute calculous cholecystitis. Delayed or improper treatment may aggravate liver damage, leading to liver failure or even death. Laparoscopic cholecystectomy (LC) is the gold standard for surgical treatment of cholecystitis with gallstones;[2,3] however, the timing of LC remains controversial. In the present study, clinical data of 60 cases of acute calculous cholecystitis with liver damage from January 2016 to January 2018 were reviewed with respect to the feasibility of LC.

2. Methods

2.1. Baseline data

From January 2016 to January 2018, 323 patients with gallstones and cholecystitis, diagnosed by abdominal color Doppler ultrasound and treated by LC, were admitted to our hospital. Of these, 60 (18.6%) patients also showed liver damage, excluding the cases caused by viral hepatitis, alcoholic liver disease, drug-induced liver damage, cirrhosis, and biliary pancreatitis. According to the timing of LC, 32 patients were assigned to the early operation group (within 72 hours after the attack) and 28 to the delayed operation group (after 72 hours post-attack). All patients signed the informed consent and were informed about the risk of the early and delayed operation. The cohort comprised of 31 males and 29 females, with an average age of 46 years. The course of disease ranged from 1 to 21 (average, 9) days. Clinical manifestations: recurrent right upper abdominal pain and abdominal distention were found in 39 cases of acute biliary colic and 18 cases of chills and fever. Liver function: 57 cases of elevated ALT (58–728 IU/L), 39 cases of elevated TBIL (26–129 μmol/L), and 46 cases of elevated GGT (68–243 IU/L). Blood routine examination: 48 cases with leukocytosis $>10.0 \times 10$–9/L. Furthermore, no severe heart, brain, lung, and kidney complications affected the surgery and treatment process in both groups. No significant difference was

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Patients were recruited in the hepatobiliary at the Peking University International hospital Research were approved and supervised by the ethics committee of Peking University International hospital. Written informed consents were obtained from all participants.

The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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detected in age, gender, and other general data between the 2 groups ($P > .05$). The patients in the 2 groups were treated with anti-infection and liver protection preoperatively and postoperatively. The patients in the early operation group were treated with LC after confirming the absence of stone in the bile duct. The patients in the delayed group were treated with LC after reexamining the liver function indices.

2.2. Diagnosis and exclusion criteria

All the patients had a history of epigastric pain before admission, and the right epigastric tenderness was positive. B ultrasound, CT, or MRCP confirmed acute calculous cholecystitis and excluded bile duct stones. Liver function examination suggested elevated bilirubin or transaminase (2/4 indices among ALT, AST, TB, and ALP were >2-fold of the normal). Disease improvement criteria: pain relief in the right upper abdomen, recovery of the liver function to normal, decrease in the number of leukocytes, and neutrophils to normal. Exclusion criteria: viral hepatitis in the active stage, liver damage caused by alcohol, drugs, immune diseases, combined with liver cirrhosis, hepatitis, and other liver diseases.

2.3. Surgical method

LC was performed by general anesthesia and conventional 3-hole operation. The operation was performed by experienced doctors to prevent the gallstones from squeezing into the common bile duct, leading to the secondary bile duct stones. The condition of the gallbladder and liver was observed intraoperatively. According to the intraoperative situation in some cases, a wedge of the liver tissue was sliced from the lower edge of the right lobe of the liver at >4 cm away from the gallbladder bed. One piece of size $0.5 \times 0.5 \times 0.5\,cm^3$ was stained by hematoxylin-eosin (HE) and examined by histopathology. The drainage tube was placed according to the intraoperative situation. The liver function and blood routine were checked several times postoperatively.

2.4. Study methods

Hematological indices, such as white blood cell count and liver function, of the 2 groups were analyzed and compared before and after LC. Also, the operation time, intraoperative hemorrhage, and incidence of complications were compared between the 2 groups.

2.5. Statistical processing

SPSS (version 18.0) software package was used. Enumeration data were analyzed by the χ^2 test, and measurement data were analyzed by the t-test. $P < .05$ was considered as statistical significance.

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Peking University international hospital ethics committee. All patients provided informed written consent.

3. Results

Operations in both groups were performed by experienced doctors without conversion to laparotomy. Among 60 LC patients, 48 cases showed acute inflammation of the gallbladder, obvious hyperemia and edema, thick and purulent bile, and hyperemia and edema in the liver and surrounding tissues. A total of 19 cases exhibited chronic inflammatory changes, cystic wall thickness, fibrous hyperplasia, adhesion of varying degrees, a little purulent bile, congestion, and edema in the liver and surrounding tissues. In the early group, 5 cases had postoperative complications; 2 cases of incision infection, 1 case of atelectasis, and 2 cases of fluid accumulation in the gallbladder fossa. In the delayed group, there were 4 postoperative complications, including 1 case of incision infection and 3 cases of effusion in the gallbladder fossa.

Histopathological results in the liver: in the 16 cases of liver biopsy, loose and fatty hepatocytes, focal degeneration, and necrosis of hepatocytes, the formation of micro abscess in the liver tissue, infiltration of a large number of inflammatory cells in the portal area, and hyperplasia of fibrous tissue were observed.

In the delayed operation group, the average time of antibiotics use was 9.5 days, the average time of liver function recovery was 10.5 days, and the length of hospital stay was 11 days. The liver function of 1 patient was not completely recovered after 22 days post-admission, but the clinical symptoms improved significantly, and the patient was discharged with medication. In the early LC group, the average time of antibiotics use was 5.5 days, the average time of liver function recovery was 7.0 days, and the average length of hospital stay was 5 days. The operation was performed successfully in both groups. The difference in the length of stay and hospitalization cost between early operation and delayed operation groups was statistically significant ($P < .05$). No significant difference was observed in the operation time, intraoperative blood loss, and postoperative complications between the 2 groups ($P > .05$) (Table 1). Also, the WBC count, total bilirubin, alanine aminotransferase, and γ-glutamyl transferase did not differ between the 2 groups at corresponding time points ($P > .05$) (Table 2).

4. Discussion

Calculous acute cholecystitis is the most common type of clinical acute abdomen. Gallstone combined with liver damage is common in the clinic, mainly manifested as abnormality in the liver function enzyme with mild jaundice. The incidence is 22%, and the degree of cholecystitis inflammation is positively related to the liver function damage.[4–6] The incidence of gallstone with liver damage was 18.6% in our center. Gallstones are embedded in the cystic duct or obstructed in the ampulla of the gallbladder. The main pathological features include obstruction of gallbladder bile excretion, blood supply disturbance of the gallbladder wall, and secondary bacterial liver damage. The causes are as follows: ① inflammation directly affects the liver tissue in cholecystitis, causes dysfunction of the liver cell based on bacterial hepatitis

Table 1

Comparison of operation between 2 groups of patients with gallstone and liver damage.

Item	Early operation group (n = 32)	Delayed operation group (n = 28)	*P* value
Time of operation (min)	39 ± 8.2	43 ± 9.7	.216
Intraoperative blood loss (ml)	10 ± 5.5	15 ± 8.8	.072
Postoperative complication (case)	5	4	.987
Average length of stay (d)	5	11	.012
Average cost of hospitalization (RMB)	8951	17021	.011

Table 2

Comparison of blood test results between 2 groups of patients with gallstone and liver damage.

Item	Early operation group (n = 32)	Delayed operation group (n = 28)	*P* value
White blood cell count			
Preoperatively	13.7 ± 1.6	12.2 ± 2.1	.113
1 day postoperatively	11.2 ± 2.4	13.1 ± 1.8	.092
3 days postoperatively	10.5 ± 1.1	11.0 ± 0.7	.077
7 days postoperatively	7.90 ± 0.8	8.30 ± 0.6	.083
Total bilirubin			
Preoperatively	33.5 ± 1.2	39.2 ± 1.3	.102
1 day postoperatively	28.2 ± 1.4	26.1 ± 1.9	.061
3 days postoperatively	18.5 ± 1.6	20.3 ± 1.1	.063
7 days postoperatively	10.2 ± 0.3	9.10 ± 0.5	.058
ALT			
Preoperatively	352.5 ± 2.6	383.9 ± 1.8	.081
1 day postoperatively	231.7 ± 1.5	272.2 ± 2.2	.073
3 days postoperatively	189.4 ± 0.9	203.4 ± 2.6	.071
7 days postoperatively	68.10 ± 1.2	59.3 ± 0.3	.067
GGT			
Preoperatively	243.3 ± 1.1	285.2 ± 2.4	.065
1 day postoperatively	199.4 ± 2.2	203.5 ± 1.3	.078
3 days postoperatively	124.9 ± 1.7	133.8 ± 1.5	.055
7 days postoperatively	78.80 ± 2.4	65.70 ± 1.9	.088

and a series of pathological changes such as liver fibrosis, cirrhosis, and fatty liver. Bacteria enter the liver through lymph circulation in cholecystitis and through the small vein of the gallbladder in cholecystitis. ② Liver infection is caused by ascension of the extrahepatic bile duct. After the toxin is absorbed by the Kupffer cells, it releases tumor necrosis factor, interleukin-1, and interleukin-6, and produces nitric oxide (NO) and free oxygen radicals, eventually leading to liver cell damage.[7]③ The inflammatory bile in the gallbladder enters the bile duct, and the stone removal causes Oddi sphincter spasm, duodenal papilledema, poor drainage of the bile, and infection spreading to the liver. When the gallbladder has acute and chronic inflammation, it loses the normal contraction function, and cannot relieve the pressure in the bile duct, thereby causing liver damage. In this study, we found that gallstone with infection is a major cause of liver damage. The peripheral blood phase reflecting the signs of infection was related to the liver function. The treatment of infection could promote the recovery of liver function, which proved that infection is also a cause of liver damage. Acute inflammation of gallstone was observed intraoperatively, and the acute inflammation of adjacent organs, the right lobe liver, and the liver portal tissue suggested severe the inflammation of the gallbladder and disrupted liver function.

Gallstone with liver damage has the following characteristics: ① It represents pain in the right upper abdomen and abdominal distention. Some patients have severe biliary colic infection, chills, and fever, and most of them have the incentive to eat greasy food. However, no clinical manifestations of viral hepatitis, such as poor appetite, fatigue, and anorexia, were observed. ② Physical examination showed tenderness in the right upper abdomen or percussion pain in the liver area, and Murphy sign was positive. In addition, no sign of chronic liver damage such as palmar erythema, spider nevus, and splenomegaly is observed. ③ ALT and GGT are the main indicators of liver damage. AST and TBIL were elevated in half of the patients. The proportions of total protein, albumin, and Albumin-globulin ratio are normal. ④ Postoperative anti-infective and liver protection treatment were given, the Symptoms improved in all patients, the liver functions of the vast majority of patients recovered satisfactorily.

Pathological results: cholelithiasis can cause liver damage, such as bacterial hepatitis, liver fibrosis, fatty liver, and liver cirrhosis. The reported pathological rate is 79% to 100%.[8] Typically, the liver damage caused by gallbladder lesions is "reactive hepatitis," and the liver lesions may recover after gallbladder lesions are removed. However, further development may result in necrosis of hepatocytes, the formation of small abscesses in the liver, and infiltration of a large number of inflammatory cells in the portal area, accompanied by different degrees of the proliferation of fibrous tissue and fibrosis.

Gallstone is one of the most common causes of liver damage. Although anti-inflammation and liver protection can improve the symptoms of liver damage during cholecystitis, the original state of the tissue may not be returned to normal only via anti-inflammatory and liver protection treatment calculous. Only active clearing of the primary lesion can solve the problem fundamentally. Different from hepatobiliary surgery, which is caused by viral hepatitis, we should take a cautious attitude, not restrict to reoperation when the liver function is completely normal. Moreover, the direct damage caused by the gallbladder to the liver should be cleared at the earliest. Reportedly, the risk of cholecystectomy in patients with liver dysfunction is increased,[8] and the data of this group showed that there was no aggravation in the liver damage in the early operation group, indicating that the impact of surgery on the body was much lower than that of bacterial liver damage caused by cholecystitis. Compared to the delayed operation group, the length of stay and cost of hospitalization in the early operation group were less than that in the delayed operation group, and hence, the liver protection treatment was administered preoperatively and postoperatively. The deterioration of liver function could be avoided by early operation.

In the acute stage of cholecystitis, the liver function has some clinical characteristics: ① the change is firstly manifested in elevated transaminase. To date, ALT and AST are considered as the "gold standards" to assess the liver cell damage.[9,10] It was observed that in the early stage of liver damage in cholecystitis, the activity of ALT and AST could be significantly increased, which is the first manifestation of altered liver function. After LC, most of the liver function was returned to normal, and the clinical symptoms were improved. ② ALP is a classic index of cholestasis. The increase in ALP is caused by the increased synthesis of hepatocytes induced by bile. ③ GGT is the most sensitive marker of biliary diseases, and its wide distribution in vivo is relatively poor for liver diseases. ④ Increased TBIL indicates that the inflammation of gallbladder is severe, and the inflammation affects the extrahepatic bile duct to cause extrahepatic cholangitis. The level of bilirubin is <171 mmol/L because it is continuously excreted through urine. However, if the bilirubin is >342 mmol/L, it often indicates serious liver parenchymal disease, accompanied by hemolysis and renal failure, which is an index of severe damage to liver function.

Intriguingly, the recurrence of gallstone with liver damage, recurrent degeneration, necrosis of liver cells, and infiltration of inflammatory cells, might lead to severe consequences, such as liver fibrosis and cirrhosis. In this study, among the 60 cases receiving surgery, 8 showed fibrosis at different degrees in the pathology of liver biopsy. Therefore, patients with gallstone, especially those with recurrent infection, should be operated at

the earliest to remove the primary lesion. This procedure can resolve the long-term repeated damage to the liver caused by gallstone cholecystitis and restore the liver function. In this study, most of the patients in the 2 groups recovered to normal within a short period, and no case of liver function damage due to LC was detected. However, for those with hepatitis, cirrhosis, and portal hypertension, the timing of LC should be set carefully to avoid the possibility of intraoperative hemorrhage or postoperative liver failure.

In Europe and other western countries, about 10% to 20% of the adults suffer from gallstones, and about 1% to 4% have acute attack symptoms every year,[11] which are not uncommon for patients with cystic calculi combined with liver function damage. The liver damage caused by calculous cholecystitis usually includes function and organ damage to the liver. Patients often have recurrent cholecystitis attacks and symptom relief. However, in the case of asymptomatic gallstone, patients might not present acute clinical manifestations of the abdomen, such as biliary colic infection or only occasionally feel discomfort in the right upper abdomen. Thus, gallstone disease is often ignored, and the history of the condition can accumulate up to decades. Although the clinical symptoms of chronic cholecystitis with gallstone and asymptomatic gallstone are not significant, pathological damage to the liver is observed, and the therapeutic effect of liver protection is often unsatisfactory.[12,13]

Taken together, gallstone combined with infection is the primary mechanism leading to liver damage. Moreover, in patients with recurrent cholecystitis, the liver exhibits pathological damage in the early stage. With the development of LC, minimally invasive LC, anti-infection, and liver protection should be performed as soon as possible, and the primary lesion should be removed. In the case of patients with chronic cholecystitis and gallstone, to reduce or avoid the pathological damage of the liver tissue, LC should also be performed in the early stage when there is no vital organ disease affecting the surgery.

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