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Observational Study

Hepatobiliary Manifestations following Two-Stages Elective Laparoscopic Restorative Proctocolectomy for Patients with Ulcerative Colitis. A prospective observational study

Hepatobiliary Manifestations after Colectomy for UC

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Abstract

BACKGROUND

Hepatobiliary manifestations occur in ulcerative colitis (UC) patients. The effect of laparoscopic restorative proctocolectomy (LRP) with ileal pouch anal anastomosis (IPAA) on hepatobiliary manifestations is debated.

AIM

This study evaluated hepatobiliary changes after Two-Stages Elective Laparoscopic Restorative Proctocolectomy for Patients with Ulcerative Colitis.

METHODS

Between June 2013 and June 2018, 167 patients with hepatobiliary symptoms underwent two-stage elective LRP for UC in a prospective observational study. Patients with ulcerative colitis and having at least one hepatobiliary manifestation who underwent LRP with IPAA were included in the study. The patients were followed up for four years to assess the outcomes of hepatobiliary manifestations.

RESULTS

The patients' mean age was 36 ±8 years, and males predominated (67.1%). The most common hepatobiliary diagnostic method was liver biopsy (85.6%), followed by MRCP (63.5%), ANCA (62.5%), US (35.9%), and ERCP (6%). The most common hepatobiliary symptom was PSC (62.3%), followed by fatty liver (16.8%) and GB stone (10.2%). 66.4% of patients showed a stable course after surgery. Progressive or regressive courses occurred in 16.8% of each. Mortality was 6%, and recurrence or progression of symptoms required surgery for 15%. Most PSC patients (87.5%) had a stable course, and only 12.5% became worse. Two-thirds (64.3%) of fatty liver patients showed a regressive course, while one-third (35.7%) showed a stable course. Survival rates were 98.8%, 97%, 95.8%, and 94% at 12, 24, 36, and at the end of the follow-up.

CONCLUSION

In patients with UC who had LRP, there is a positive impact on hepatobiliary disease. It caused an improvement in PSC and FLD. The most prevalent unchanged course was PSC, while the most common improvement was fatty liver status.

Key Words: Courses; Hepatobiliary manifestations; Primary sclerosing cholangitis; Restorative proctocolectomy

Core Tip: There has been little research on the efficacy of proctocolectomy in ulcerative colitis patients with hepatobiliary manifestations. The course of hepatobiliary symptoms after proctocolectomy is being evaluated prospectively in our study. The main finding of this study was that two-thirds of patients had an unchanged course following surgery, whereas 16.8% had a progressive or regressive course. The mortality rate was 6%, and 15% of patients required surgery due to recurrence or worsening symptoms. Most PSC patients (87.5%) had an unchanged course, with only 12.5% progressing. Two-thirds (64.3%) of fatty liver patients progressed, whereas one-third (35.7%) remained stationary. At 12, 24, 36, and 48 mo, the survival rates were 98.8%, 97%, 95.8%, and 94%, respectively.

INTRODUCTION

Inflammatory bowel disease (IBD) is expected to affect 1% of the population over the next decade [1]. Although the primary clinical manifestations of IBD are centred on the

gastrointestinal tract, 25–40% of IBD patients develop at least one extraintestinal manifestation (EIM) [2].

Hepatobiliary manifestations constitute one of the most common EIMs in IBD [3]. Primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), fatty liver, cholelithiasis, primary biliary cholangitis, portal vein thrombosis, and hepatic abscess are the most prevalent hepatobiliary manifestations of ulcerative colitis (UC). [4-5].

Most UC patients can be managed with medications, but minorities require proctocolectomy [6]. Two-stage laparoscopic proctocolectomy (LRP) with ileal pouch-anal anastomosis (IPAA) is a cure for UC, but its effect on hepatobiliary diseases is controversial [6-10]. Therefore, we conducted a prospective observational study to examine the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression.

MATERIALS AND METHODS

2.1 Study design and participants:

This is a prospective observational study on 167 patients with hepatobiliary manifestations who underwent two-stage elective LRP with IPAA for UC from June 2013 to June 2018 at a university hospital. Inclusion criteria were all patients between 18 and 69 years; men and women with at least one hepatobiliary manifestation. In patients with UC, surgery was decided according to The European Crohn's and Colitis Organisation (ECCO) guidelines on therapeutics in UC [11]. Exclusion criteria included: alcohol abuse, severe heart failure or type II diabetes mellitus, complications or death related to LRP operation, liver toxicity of IBD-related medications, active or chronic viral hepatitis, hemochromatosis, Wilson's disease, drugs-induced steatosis (amiodarone or tamoxifen), morbid obesity or patients undergoing bariatric surgery, immunoglobulin G4-related cholangitis; human immunodeficiency virus (HIV)/acquired immune deficiency syndrome; tuberculosis; secondary sclerosing cholangitis; cholangiocarcinoma; complications of advanced PSC (hepatic encephalopathy, portal hypertension, hepatorenal syndrome, or hepato-pulmonary

syndrome; end-stage liver failure), hypercoagulability status (SLE, increased von Willebrand factor or increased homocysteine level), oral contraceptive pills, Grave's disease, dyslipidemia, and previous biliary tract surgery including cholecystectomy.

2.2 Study ethics:

The Institutional Review Board approved the study (ZU IRB#9841). Each patient signed a written consent form, and the study followed the rules of the 1975 Declaration of Helsinki principles. In addition, the study was registered on ClinicalTrials.gov (NCT05495178) and done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.3 Definitions of outcomes and measurements:

PSC is progressive biliary fibrosis affecting intra and/or extrahepatic bile ducts [12] and diagnosed by laboratory tests [(cholestasis, Antineutrophil cytoplasmic antibodies (ANCA)], radiology [abdominal ultrasonography, abdominal computed tomography (CT), (ERCP), or (MRCP)], and liver biopsy. Primary biliary cholangitis (PBC) is characterized by the loss of small and medium-sized bile ducts on liver biopsy, elevated anti-mitochondrial antibodies, and altered GGT and ALP levels [13]. Non-alcoholic fatty liver disease (NAFLD) is characterized by fat storage in ≥ 5% of hepatic steatosis in the absence of concomitant liver disease (chronic viral hepatitis), use of steatosis-inducing medications (amiodarone or tamoxifen), autoimmune hepatitis, hemochromatosis, Wilson's disease, or excessive alcohol consumption [14]. Diagnosis of NAFLD was made by liver biopsies or US [15], and the severity score was previously stated [16]. Autoimmune hepatitis diagnosis based on the International Autoimmune Hepatitis Group criteria with a score of >15 points consisting of demographic, histologic, and laboratory markers, including antinuclear antibodies with a titer of at least 1:40 and liver histology [17]. An aseptic liver abscess (AA) is diagnosed based on IBD history, US, and CT [18]. Ultrasound, colour Doppler, and/or CT scans were used to detect portal vein thrombosis.

2.4 Perioperative technique and follow-up after surgery:

For patients with UC who require surgery, two stages of LRP with IPAA and a diverting loop ileostomy are the gold standard [19]. The diverting loop ileostomy was reversed 2-3 mo following surgery. Because of the increased risk of thromboembolic events, prophylactic anticoagulation medication was scheduled and continued for six months after surgery. The follow-up period was four years, and cases lost during the follow-up period were excluded from the study.

Follow-up with the clinical progression of patients' conditions and laboratory evaluations was performed at six months, one year, two years, three years, and four years, or at any time of patients' complaint. These data were compared to data obtained immediately before surgery (at the time of surgery). Follow-ups were performed at outpatient clinics, *via* phone, or by email. Laboratory (LFT, antibodies, CA19-9) and radiology (abdominal ultrasonography, colour Doppler, CT, MRCP) tests were performed as part of the follow-up assessments. An endoscopic examination of the ileal pouch on an annual basis was arranged. A liver biopsy was planned at the end of the study.

2.5 Statistical methods:

Version 28 of SPSS was used for data management and statistical analysis (IBM, Armonk, New York, United States). The normality of quantitative data was evaluated using the Kolmogorov–Smirnov test, the Shapiro-Wilk test, and direct data visualization methods. Means and standard deviations, or medians and ranges based on normality tests, were used to summarize the quantitative data. As a summary of categorical data, numbers and percentages were used. The McNemar test compared laboratory and clinical findings before and after surgery. We used a Kaplan-Meier analysis to estimate overall survival and recurrence-free survival. The independent t-test or the Mann-Whitney U test for normally and non-normally distributed quantitative variables was used to compare the regression rates of hepatobiliary

manifestations in the two groups. We compared categorical data using the Chi-square test. Multivariate logistic regression analysis was done to predict no regression of hepatobiliary manifestations. Each significant variable on the univariate levels was included in a multivariate regression model and adjusted for age, gender, smoking, family history of ulcerative colitis, and ulcerative colitis duration. The odds ratios and confidence intervals at 95 % were calculated. All statistical tests were two-sided. P values < 0.05 were considered statistically significant.

RESULTS

Figure 1 shows the flow diagram of the inclusion and exclusion criteria of the study cohort.

3.1 General characteristics:

As shown in Table 1, the mean age was 36 ± 8 years, with male predominance (67.1%). The most frequent diagnostic method for hepatobiliary manifestations was liver biopsy (85.6%), followed by MRCP (63.5%), ANCA (62.5%), US (35.9%), and ERCP (6%). Figure 2 shows showed the frequency of different hepatobiliary manifestations.

3.2 Outcomes:

After surgery, there were clinical and laboratory improvements (Table 2, Figure 3A-B). Figure 4A-B showed that 66.4% of patients had a stationary course. In comparison, 16.8% of patients showed a progressive or regressive course, and there are variations in the courses of different types of hepatobiliary manifestations.

3.3 Overall survival and recurrence-free survival using Kaplan-Meier analysis:

The survival rate was 98.8%, 97%, 95.8%, and 94% at 12 mo, 24 mo, 36 mo, and at the end of the follow-up. Regarding the recurrence or progression of symptoms requiring surgery, the recurrence-free rate at 12 mo was 98.2%. At 24 mo, it was 92.8%. At 36 mo, it was 89.2%. At the end of the follow-up, it reached 85% (Figure 5).

3.4 Factors affecting regression of hepatobiliary manifestations:

Patients with no regression (stationary and progressive course) demonstrated higher use of anti-TNF (15.1% vs. 0%, $P = 0.028$), corticosteroids (43.2% vs. 17.9%, $P = 0.012$),

and hepatobiliary treatment (80.6% *vs* 7.1%, P < 0.001). In addition, they demonstrated higher percentages of high ALT (74.8 *vs* 39.3%, P < 0.001), high AST (75.5% *vs* 57.1%, *P* = 0.047), high alkaline phosphatase (71.2% *vs* 3.6%, P < 0.001), jaundice (67.6% *vs* 46.4%, *P* = 0.033), pruritus (59% *vs* 14.3%, P < 0.001), and fever (24.5% *vs* 3.6%, *P* = 0.013). Age (*P* = 0.578), gender (*P* = 0.327), smoking (*P* = 0.780), family history (*P* = 0.278), duration of UC (*P* = 0.877), treatment for UC (*P* = 0.601), family history of PSC (*P* = 0.079), pain (*P* = 0.496), and fatty liver score (*P* = 0.121) were not found to be significantly different (Table 3).

3.5 Prediction of no regression of hepatobiliary symptoms:

The predictors of no regression were steroid treatment (OR = 3.68, 95%CI = 1.29 – 10.45, *P* = 0.015), high ALT (OR = 5.39, 95%CI = 2.19 – 13.28, P < 0.001), high AST (OR = 2.59, 95%CI = 1.08 – 6.2, *P* = 0.032), high ALP (OR = 73.59, 95%CI = 9.52 – 568.93, P < 0.001), high bilirubin (OR = 2.72, 95%CI = 1.16 – 6.4, *P* = 0.022), jaundice (OR = 2.49, 95%CI = 1.07 – 5.8, *P* = 0.034), pruritus (OR = 9.75, 95%CI = 3.12 – 30.5, P < 0.001),and fever (OR = 9.7, 95%CI = 1.25 – 75.03, *P* = 0.029). The predictors with their odds ratios and 95% confidence intervals are illustrated in Table 4.

DISCUSSION

To the best of our knowledge, this is the first current study to investigate the course of hepatobiliary symptoms in patients with UC after elective two-stage LRP with IPAA. Colectomy was correlated to a considerably low rate of progressive course in this study of 167 patients: 66.4% for an unchanged course, 16.8% for a regressive course, and 16.8% for a progressive course. There were not many changes for PSC (91/104, 87.5%), while the most progressive cases were gallbladder disorders (12/17, 70.5%), and the most regressive cases were fatty liver (18/28, 64.3%).

Many theories have been proposed to explain the course of PSC after LRP with IPAA, including autoimmune phenomena [20], liver-gut crosstalk [21], the influence of saturated fat on changes in the bile acid pool, with an increase in the taurocholic acid [22], and bacterial translocation or absorption of bacterial endotoxins into the portal

circulation *via* a chronically inflamed bowel with Kupffer cell activation [23-26]. The effects of colectomy on PSC have been documented in conflicting ways. Colectomy was beneficial according to a study by Lepisto *et al* that stated that PSC severity increased in four (13%) patients, regressed in 15 (50%), and stayed stationary in 11 (37%) [6]. Regarding the incidence of progression, our findings are identical to those of this study, but not in the incidence of stationary and regressive courses. Our stationary course of PSC is higher (87.5% vs. 37%), and none of the cases in our study demonstrated a regression course. We performed liver biopsies and MRCP on all PSC patients prior to surgery and during the follow-up period, whereas the previous study relied on liver function for diagnosis and did not perform liver biopsies on all patients. Furthermore, our study had a large number of patients, and cases lost to follow-up were excluded from our study (in comparison to earlier study). Our study's higher stable course of PSC may be attributable to Ursodeoxycholic acid (UDCA) (15 mg/kg/day) in all patients after LRP, whereas only 9/30 patients had UDCA following colectomy in the prior study. Treatment with UDCA has a beneficial effect on the course of PSC; studies have demonstrated efficacy [27-30]. A good proportion of PSC cases not progressing to a more severe form is associated with the absence of pouchitis in all of our patients' ileoanal pouch anastomosis. The study corroborated our conclusion that pouchitis may aggravate PSC [31].

In contrast, another study by Aitola *et al.* stated that proctocolectomy exerted no beneficial effect on PSC, the stage of which has remained unchanged or has progressed with no statistically significant improvements in liver function test values [7]. On the contrary, our results showed a statistically significant improvement in liver function test values after surgery. Variations in the results could be attributed to methodological differences, diagnostic procedures (liver biopsy in 71% of cases only), and the number of cases. Perhaps, the effect of LRP on PSC is beneficial, as evidenced by the higher percentage of stable disease and smaller progressive cases. Another study by Treeprasertsuk *et al.* discovered that proctocolectomy had no benefit and a lower survival rate than expected. They experienced only progressive courses with higher

mortality rates; LCF, acute cholangitis, right hepatic vein thrombosis with liver infarcts, and many cases that needed liver transplantation [32]. The poor prognosis could be attributed to the study's small sample size, open approach, surgical difficulties, and heterogeneity in selection criteria, particularly the inclusion of cirrhotic patients with low platelet counts and albumin levels.

In patients with LRP, resection of a short segment of the ileum and the entire colon inhibits bile acid absorption, resulting in supersaturation of biliary cholesterol [8], pouch metaplasia with decreased primary bile acid absorption [33], and delayed gall bladder emptying [34]. We found a high incidence of recurrent biliary colic requiring surgery (12/17, 70.5%), while the remaining five cases had a stationary course without symptoms. Concomitant cholecystectomy with LRP may prolong the operative time (nearly 40 minutes) and add more risk of complications. However, it saves the patient from going through more difficult cholecystectomy operation / gallstone complications in the future [35]. There were no cases of gallbladder cancer in our study. This is because most gallstone cases develop symptoms following LRP, necessitating cholecystectomy. Another problem is the short duration of follow-up (4 years).

Multiple studies showed that proctocolectomy could help with fatty liver regression [7, 36-37]. We agree with prior evidence that proctocolectomy is favourable for NAFLD. LRP had a positive effect on fatty liver, with 18 cases (18/28, 64%) showing complete regression to normal liver and the remaining ten patients (36%) showing a stationary course. This improvement is due to improvements in malnutrition, anaemia, and a reduction in corticosteroid dosage during the surgical follow-up period, as supported by a study [38]. NAFLD progression was not observed in our cases due to the absence of pouchitis. As a result, we concluded that proctocolectomy plays a definitive role in the management of NAFLD-complicating ulcerative colitis, as evidenced by radiology and liver biopsy (improvement of fatty liver score from a median of 2 (range 1-3) in preoperative biopsies to a median of 1 (range 0-3) in postoperative biopsies).

High incidence of PVT in IBD may be due to increased factors V and VIII levels, platelet counts, fibrinogen levels, or decreased antithrombin III levels [39-40]. In our study, we

identified six patients with PVT: four cases before surgery, no recurrence after surgery, and two patients who developed PVT after surgery. One of the two postoperative PVT cases exhibited partial portal vein obstruction, which was treated with anticoagulants. In contrast, the second case exhibited complete obstruction of PVT with intestinal gangrene, necessitating resection of the majority of the small intestine with short bowel syndrome, and died two months later. The low incidence of postoperative PVT can be due to the small number of cases, the routine use of low molecular heparin in the postoperative period for six months in all cases according to the current society guidelines and expert opinion [40], absence of pouchitis which increases the incidence of PVT [41], and the possible occurrence of PVT not associated with specific symptoms or asymptomatic [42]. The use of abdominal ultrasound and colored Doppler at regular intervals unquestionably aided in detecting asymptomatic cases. We concluded that proctocolectomy decreases the incidence but not the severity of PVT with an unfavorable outcome, despite the small number of cases, with a mortality rate of 50% among those who developed PVT is similar to the findings of other studies [43].

Two isolated PBC accidentally discovered cases were included; one regressed to normal liver condition, while the other progressed to liver cell failure and required liver transplantation without mortality. We thought that the excellent prognosis was due to obeticholic acid (OCA) that improved the course of the disease [44], removal of the colon, the site of antibody production, which helped make the prognosis better after surgery, and absence of pouchitis [9].

One patient with UC developed a liver abscess before surgery, whereas no such case was reported after LRP. We concur with the pathogenesis that liver abscess may be caused by antibodies produced by patients with UC attacking the liver, resulting in necrosis and abscess formation that was negative for bacteria [45]. Proctocolectomy permanently eliminates the site of antibody production. Furthermore, postoperative corticosteroids help to prevent recurrence [46]. Proctocolectomy prevents liver abscesses, according to our findings.

One case of AIH was diagnosed before surgery and regressed to normal following LRP with a favourable prognosis, demonstrating the positive effects of proctocolectomy [47]. The favorable prognosis of our patient was likely due to the removal of the inflamed colon and steroid-based immunosuppressive therapy [48].

An earlier study confirmed the efficacy of proctocolectomy for nonspecific reactive hepatitis [7]. In accordance with the previous study's findings, we diagnosed 8 patients with nonspecific reactive hepatitis, and complete regression in every case was confirmed.

Strengths and Limitations:

This is a large prospective multicenter study of different hepatobiliary manifestations assessment after LRP with a relatively long duration of patient follow-up. We also included comprehensive clinical points evaluating different courses of hepatobiliary manifestations. A prospective study prevents selection bias with accurate results that could be generalized.

However, our study has some limitations. One is the lack a control group of patients that were not operated on. Therefore, this study did not handle the severity of preoperative colitis and its effect on the course of hepatobiliary manifestations in the postoperative period. Another limitation is that it did not evaluate the disease course after liver transplantation. Another limitation is that we did not evaluate the treatment of both UC and hepatobiliary manifestations during the postoperative course. Finally, we did not evaluate the causes of the high incidence of symptomatic gallbladder stones.

CONCLUSION

Patients with UC and hepatobiliary manifestations operated with restorative LRP had different postoperative hepatobiliary manifestations courses. PSC showed the most common stationary forms, while the fatty liver was the most common with a regressive course. Surgery does not affect the hepatobiliary manifestations negatively in most

patients. <u>Further studies are required to compare the outcome of hepatobiliary manifestations after surgery with those after medical treatment.</u>

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD) is expected to affect 1% of the population over the next decade . Hepatobiliary manifestations constitute one of the most common extraintestinal manifestations in inflammatory bowel disease. Primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), fatty liver, cholelithiasis, primary biliary cholangitis, portal vein thrombosis, and hepatic abscess are the most prevalent hepatobiliary manifestations of ulcerative colitis (UC).Most UC patients can be managed with medications, but minorities require proctocolectomy .

Research motivation

Two-stage laparoscopic proctocolectomy (LRP) with ileal pouch-anal anastomosis (IPAA) is a cure for UC, but its effect on hepatobiliary diseases is controversial .

Research objectives

Therefore, we conducted a prospective observational study to examine the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression.

Research methods

This is a prospective observational study on 167 patients with hepatobiliary manifestations who underwent two-stage elective LRP with IPAA for UC We examined the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression

Research results

the course of hepatobiliary manifestations after surgery is improved in most forms. Most PSC patients had a stable course, Two-thirds of fatty liver patients showed a regressive course with an improved survival rate at the end of the study.

Research conclusions

our study emphasized the positive and improving effects of surgery on hepatobiliary manifestations in patients with ulcerative colitis

Research perspectives

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further studies are required in a larger sample size to evaluate the effect of surgery on different forms of hepatobiliary manifestations in patients with ulcerative colitis. further studies are required to compare the effect of surgery and effects of medical treatment

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