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Retrospective Study**Clinical significance of half-hepatic blood flow occlusion technology in patients with hepatocellular carcinoma with cirrhosis****Abstract****BACKGROUND**

Most patients with primary hepatocellular carcinoma (HCC) have a history of chronic hepatitis B and usually present with varying degrees of cirrhosis. Owing to the special nature of liver anatomy, the blood vessel wall in the liver parenchyma is thin and prone to bleeding. Heavy bleeding and blood transfusion during hepatectomy are independent risk factors for liver cancer recurrence and death. Various clinical methods have been used to reduce intraoperative bleeding, and the Pringle method is most widely used to prevent blood flow to the liver.

AIM

To investigate the effect of half-hepatic blood flow occlusion after patients with HCC and cirrhosis undergo hepatectomy.

METHODS

This retrospective study included 88 patients with HCC and liver cirrhosis who underwent hepatectomy in our hospital from January 2017 to September 2020. Patients were divided into two groups based on the following treatment methods: the research group ($n = 44$), treated with half-hepatic blood flow occlusion technology and the control group ($n = 44$), treated with total hepatic occlusion. Differences in operation

procedure, blood transfusion, liver function, tumor markers, serum inflammatory response, and incidence of surgical complications were compared between the groups.

RESULTS

The operation lasted longer in the research group than in the control group (273.0 ± 24.8 min *vs* 256.3 ± 28.5 min, $P < 0.05$), and the postoperative anal exhaust time was shorter in the research group than in the control group (50.0 ± 9.7 min *vs* 55.1 ± 10.4 min, $P < 0.05$). There was no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the research and control groups ($P > 0.05$). Before surgery, there were no significant differences in serum alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, and prealbumin levels between the research and control groups ($P > 0.05$). Conversely, 24 and 72 h after the operation the respective serum ALT (378.61 ± 77.49 U/L and 246.13 ± 54.06 U/L) and AST (355.30 ± 69.50 U/L and 223.47 ± 48.64 U/L) levels in the research group were significantly lower ($P < 0.05$) than those in the control group (ALT, 430.58 ± 83.67 U/L and 281.35 ± 59.61 U/L; AST, 416.49 ± 73.03 U/L and 248.62 ± 50.10 U/L). The operation complication rate did not significantly differ between the research group (15.91%) and the control group (22.73%; $P > 0.05$).

CONCLUSION

Half-hepatic blood flow occlusion technology is more beneficial than total hepatic occlusion in reducing liver function injury in hepatectomy for patients with HCC and cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 90% of all primary liver tumors^[1]. Most patients with HCC often also have cirrhosis, and the recurrence of microvascular tumor thrombi has been increasing. Currently, radical surgery is the preferred treatment for

HCC; however, massive intraoperative bleeding⁴ and blood transfusion may increase the incidence of postoperative complications, mortality, and the possibility of recurrence and metastasis of HCC^[2,3]. The vascular distribution of the liver is more complex, and the blood supply is rich. Therefore, effective control of bleeding during hepatectomy has been the focus of liver surgery research^[4]. In 1988, researchers proposed a method of vascular occlusion during hepatectomy that could be used to control intraoperative blood loss. The classical Pringle total hepatic occlusion and selective semi-hepatic occlusion techniques are mainly used in clinical practice^[5]. However, there are differences in the selection of different blood-flow blocking techniques during tumor surgery. This study selected patients with HCC and liver cirrhosis scheduled to undergo hepatectomy in our hospital to explore the postoperative surgical effect of half hepatic blood flow occlusion and liver function recovery in this patient population.

MATERIALS AND METHODS

General data

This retrospective single-blinded study included 88 patients with HCC and liver cirrhosis who underwent hepatectomy from January 2017 to September 2020 in our hospital and were divided into an observation group and a control group (44 patients in each group). The inclusion criteria were based on the diagnostic criteria for patients with HCC in the code for the diagnosis and treatment of primary liver cancer (2011 edition)^[6] as follows: confirmed preoperative computed tomography and magnetic resonance imaging examinations or confirmed liver biopsy, age of ≤ 75 years, mild cirrhosis, preoperative Child-Pugh liver function grade A or B^[7], and tumor diameter of 2.0–6.0 cm. This study met the relevant requirements of the Medical Ethics Committee, and written informed consent was obtained from the patients. The exclusion criteria were as follows: patients with metastasis to other abdominal organs, with other malignant tumors, history of cerebrovascular or myocardial infarction within the last 6 mo, with history of parasitic diseases such as liver echinococcosis, and with anemia or malnutrition.

The research group included patients aged 50–75 years, with an average age of 60.6 ± 5.0 years (26 men and 18 women). Forty patients had preoperative Child-Pugh grade A and four patients had grade B. The mean lesion diameter was 5.18 ± 1.00 cm. History of hepatitis B virus infection was noted in 32 cases. The mean serum alpha-fetoprotein (AFP) value was 240.8 ± 75.6 ng/L. Regarding the surgical resection scope, there were ≥ 3 Liver segments in 18 cases and < 3 Liver segments in 26 cases. The control group included patients aged 48–75 years, with an average age of 61.3 ± 5.5 years (22 men and 22 women). Thirty-seven patients had preoperative Child-Pugh grade A and seven patients had grade B. The mean lesion diameter was 5.08 ± 1.30 cm. History of hepatitis B virus infection was noted in 27 cases, and the mean serum AFP value was 228.6 ± 66.3 ng/L. Regarding the surgical resection scope, there were ≥ 3 Liver segments in 14 cases and < 3 liver segments in 30 cases. There was no statistically significant difference in the baseline data between the groups ($P > 0.05$), as shown in Table 1.

Operation methods

All patients underwent a right upper abdominal incision under general anesthesia. The site of the lesion and scope of resection were determined after entering the abdomen. All liver tissues were removed using forceps, and the duct with a larger wound surface was sutured and tied.

The control group was treated with the Pringle total hepatic blood flow occlusion technique, in which partial hepatectomy was performed after the hepatoduodenal ligament and entire hepatic blood flow were blocked with a normal drainage tube through the Venturi hole tightly the hepatoduodenal ligament to completely block the hepatic artery and portal vein. Every operation was controlled for 15 min, depending on the ease of operation and adjustment of the block number of operating time. If the liver tumor could not be removed within the period of closure, the operation had to be repeated for 5–10 min intermittently until the liver tumor was removed and blocked at most twice.

Half-hepatic blood flow occlusion technology was used in the research group. The first hepatic portal was dissected, and the left and right hepatic veins, left and right portal veins, and left and right hepatic ducts were bluntly separated to block the branches of the hepatic artery and portal vein on the affected side to form a local ischemic area. Hepatectomy was performed along the edge of this ischemic area. Vascular forceps were used to externally separate the hilum at the upper margin of the lateral sulcus of the affected side against the Glisson sheath. The fingers of the left hand were guided behind the hepatic portal, and the vascular forceps were threaded out from behind the Glisson sheath and blocked the affected side of the liver into the hepatic blood flow with the blocking band, for < 15 min each time, and blocked again 5 min after opening. After liver resection, the wound was treated, the blood flow pathway was opened, and an abdominal drainage tube was placed.

Observation indicators and detection methods

Operation time, incision length, surgical bleeding, portal block time, postoperative anal exhaust time, drainage tube indwelling time, and hospital stay were compared between the groups. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), prealbumin (PA), AFP, carcinoembryonic antigen (CEA), α -L fassosylase (AFU), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) levels before and after surgery, C-reactive protein (CRP) levels, and postoperative complications were also compared between the groups.

After surgery, 5 mL fasting venous blood was collected from the patient and centrifuged at 3000 rpm for 5 min; the supernatant was collected to detect serum ALT, AST, TBIL, and PA levels. TBIL levels were determined using the vanadate method. The kit was provided by Beijing Jiuqiang Biotechnology Co., Ltd. The normal reference range was 3.0–20.0 μ mol/L. AST and ALT were continuously monitored by Ningbo Purui Biotechnology Co., LTD., with the normal reference range being 0–40 U/L. The PA immunotransmission turbidimetry kit was provided by Shanghai Shenfeng Biological Reagent Co., Ltd., with a normal reference range of 200–400 mg/L. The levels

of AFP, AFU, and CEA in the serum were detected using a C6000 automatic immunochemiluminescence analyzer provided by Roche. All operations were carried out in strict accordance with the requirements of the kit manufactured by Wuhan Youersheng Bioengineering Co., LTD. The normal reference values of the tumor markers were: AFP < 15 ng/mL, AFU < 40 U/L, CEA < 5.0 ng/mL, and CA19-9 < 27 U/L.

Statistical analysis

SPSS 21.0 was used for data analysis. ALT, AST, TBIL, and other measurement data of the two groups are expressed as mean \pm SD, and the *t*-test was used for inter-group comparisons. For enumeration data, the χ^2 test was used for inter-group comparisons. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of surgical process indicators between the two groups

The operation group in the research group was longer than that of the control group ($P < 0.05$). Postoperative anal exhaust time in the research group was shorter than that in the control group ($P < 0.05$), with no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the operation group and the control group ($P > 0.05$, Table 2).

Comparison of liver function indexes between two groups of patients

Before surgery, there were no significant differences in serum ALT, AST, TBIL, and PA levels between the research and control groups ($P > 0.05$). Meanwhile, 24 h and 72 h after operation, the serum ALT and AST values in the research group were lower than those in the control group ($P < 0.05$, Table 3).

Comparison of tumor marker levels between the two groups

Before surgery, there were no significant differences in serum AFP, CEA, and AFU levels between the research group and the control group ($P > 0.05$). One month after surgery, the serum AFP, CEA, and AFU levels in the two groups were lower than those before surgery ($P < 0.05$), and there was no statistically significant difference between the two groups ($P > 0.05$, Table 4).

Comparison of inflammatory factors between the two groups of patients before and after surgery

Before surgery, there were no significant differences in serum TNF- α , IL-6, and CRP levels between the research and control groups ($P > 0.05$). The levels of TNF- α and IL-6 in the research group were lower than those in the control group ($P < 0.05$, Table 5).

Comparison of operation complication rate between the two groups

The operation complication rate of the research group was 15.91%, whereas that of the control group was 22.73%, and the difference was not statistically significant ($P > 0.05$, Figure 1).

DISCUSSION

Total hepatic blood flow occlusion during surgical resection can completely block blood return to the portal vein system, resulting in gastrointestinal tract hyperemia, impaired mucosal barrier function, and high susceptibility to bacterial and toxin infections. Long-term blocking of portal blood flow can lead to portal vein and superior mesenteric vein thromboses^[8-10]. More importantly, the blood entering the liver causes ischemic reperfusion injury of the liver parenchyma and distal organs after the blood flow is restored, and the liver function is seriously impaired. Theoretically, local hemo-occlusion in the affected segment of the patient's liver is better, with minimal damage to liver function and in line with the concepts of anatomic hepatectomy and precise hepatectomy^[11-13]. However, the operation process is complicated and requires mastery of color ultrasound-guided puncture technology, which has not been popularized.

Although half-hepatic blood flow occlusion technology cannot directly block local liver blood flow from entering the liver, it retains all blood supply to the healthy side of the liver, and intraoperatively greatly reduces healthy-side liver parenchyma ischemia-reperfusion injury, causing minor damage to the liver; after surgery, liver function can be quickly restored, which is obviously advantageous in operations for hepatitis and hepatocirrhosis^[14-17].

Our study showed that the operation lasted longer in the research group than in the control group. There was no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the operation and control groups, indicating that control of half-hepatic blood flow during the operation was similar to that during use of the complete hepatic occlusion technique, which could effectively reduce bleeding. The half-hepatic blood flow occlusion technique requires detailed intrathecal dissection of the first hilum of the liver, thus increasing the difficulty of the operation and the operative time. The technique of hepatic blood flow occlusion for hepatectomy can easily lead to liver ischemia and hypoxia, which can cause liver tissue damage and liver function impairment^[18]. Meanwhile, 24 and 72 h after the operation, the serum ALT and AST levels in the research group were significantly lower than those in the control group, indicating that the half-hepatic blood flow occlusion technique is superior for postoperative liver function recovery. The reason is that half-hepatic occlusion does not markedly influence the hemodynamics, and the mesenteric blood still flows back to the systemic circulation, avoiding gastrointestinal hyperemia, intestinal bacterium and endotoxin translocation, intestinal ventricular membrane injury, and liver regeneration. After operation, healthy hepatic arteries and portal veins remain open, not affecting the blood supply, thus avoiding ischemia-reperfusion injury and having less impact on liver function, especially in patients with hepatocirrhosis and other liver-related diseases. The rate of surgical complications in the research group was lower than that in the control group. This may be because the single block time of the half-hepatic blood flow occlusion technique is long, and the portal vein and hepatic artery branches at the

lesion site are directly ligated or even separated; therefore, there is sufficient time for liver parenchyma dissection, hemostasis of the liver section, and bile leakage of the section to reduce the occurrence of surgical complications. In the past, the clinical diagnosis of patients with liver cancer was mainly based on AFP levels. Although the operation was simple, the detection sensitivity was not high, and it was easy to miss the diagnosis. In this study, 1 mo after surgery, the levels of serum AFP, CEA, and AFU in both groups were lower than those before surgery ($P < 0.05$), and there was no statistically significant difference between the groups. The reason for the analysis was that the patients were relieved of tumor cell growth and other factors after surgery, and the expression levels of AFP, AFU, and CEA decreased significantly.

Hepatectomy has always been the primary choice for patients with HCC and liver cirrhosis. Intraoperative blood flow occlusion with a half approach to the liver and a complete approach to the liver are both safe and effective, and the choice between the two methods is controversial^[19,20]. Therefore, the two methods were compared in this study. Changes in the operation process indicators were compared after the patients with hepatocirrhosis received different treatments. Postoperative liver function recovery and the occurrence of adverse reactions had certain reference values. Although half-hepatic blood flow occlusion is complicated and can prolong the operation time, it causes limited damage to liver function during the operation and is beneficial for the recovery of liver function after surgery, rendering it worthy of widespread clinical application. However, the sample size of this study was relatively small, and it is necessary to increase the sample size and detection indicators in future studies to verify the reliability of the results of this study.

CONCLUSION

In conclusion, half-hepatic blood flow occlusion technology is more beneficial than total hepatic occlusion in reducing liver function injury in patients with HCC and cirrhosis undergoing hepatectomy.

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Figure Legends

Figure 1 Histogram of complications in the two groups.

Table 1 Comparison of baseline data between the two groups of patients, *n* (%)

Normal information	Research group (<i>n</i> = 44)	Control group (<i>n</i> = 44)	<i>t</i> / χ^2 value	<i>P</i> value
Age (yr)	60.6 \pm 5.0	61.3 \pm 5.5	-0.625	0.534
Lesion diameter (cm)	5.18 \pm 1.00	5.08 \pm 1.30	0.404	0.687
Serum AFP (ng/L)	240.8 \pm 75.6	228.6 \pm 66.3	0.805	0.423
Sex			0.733	0.392
Male	26 (59.09)	22 (50.00)		
Female	18 (40.91)	22 (50.00)		
Child-Pugh stage			1.252	0.263
A stage	40 (100)	37 (84.09)		
B stage	4 (9.09)	7 (15.91)		
Hepatitis B virus infection			1.286	0.257
Yes	32 (72.73)	27 (61.36)		
No	12 (27.27)	17 (38.64)		
Surgical resection range			0.786	0.375
\geq 3 liver segments	18 (40.91)	14 (31.82)		
< 3 liver segments	26 (59.09)	30 (68.18)		

Table 2 Comparison of surgical process indicators between the two groups (mean \pm SD)

Index	Research group (<i>n</i> = 44)	Control group (<i>n</i> = 44)	<i>t</i> value	<i>P</i> value
Operation time (min)	273.0 \pm 24.8	256.3 \pm 28.5	2.932	0.004
Incision length (cm)	25.98 \pm 1.55	26.14 \pm 1.64	-0.470	0.639
Surgical bleeding (mL)	626.9 \pm 105.1	598.4 \pm 97.0	1.322	0.190
Portal block time (min)	25.3 \pm 4.1	23.5 \pm 4.5	1.961	0.053
Postoperative anal exhaust time (h)	50.0 \pm 9.7	55.1 \pm 10.4	-2.379	0.020
Drainage tube indwelling time (d)	3.84 \pm 0.66	3.62 \pm 0.71	1.505	0.136

Hospital stay (d)	13.6 ± 1.8	14.0 ± 2.2	-0.933	0.353
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Table 3 Comparison of liver function indexes between the two groups of patients (mean ± SD)

Index	Research group (n = 44)	Control group (n = 44)	t value	P value
ALT (U/L)				
Preoperative	33.04 ± 8.56	34.72 ± 8.11	-0.945	0.347
24 h after operation	378.61 ± 77.49 ^a	430.58 ± 83.67 ^a	-3.023	0.003
72 h after operation	246.13 ± 54.06 ^a	281.35 ± 59.61 ^a	-2.903	0.005
AST (U/L)				
Preoperative	29.61 ± 7.21	27.30 ± 7.85	1.438	0.154
24 h after operation	355.30 ± 69.50 ^a	416.49 ± 73.03 ^a	-4.026	0.000
72 h after operation	223.47 ± 48.64 ^a	248.62 ± 50.10 ^a	-2.389	0.019
TBIL (μmol/L)				
Preoperative	15.92 ± 4.40	15.28 ± 4.71	0.659	0.512
24 h after operation	32.85 ± 7.01 ^a	34.06 ± 8.43 ^a	-0.732	0.466
72 h after operation	20.46 ± 5.83 ^a	22.90 ± 6.15 ^a	-1.910	0.059
PA (mg/dL)				
Preoperative	313.86 ± 46.91	320.74 ± 51.67	-0.654	0.515
24 h after operation	194.82 ± 32.65 ^a	188.57 ± 29.48 ^a	0.942	0.349
72 h after operation	275.12 ± 41.81 ^a	269.84 ± 46.10 ^a	0.563	0.575

^aP < 0.05 vs this group before surgery.

ALT: Alanine transaminase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; PA: Prealbumin.

Table 4 Comparison of tumor marker levels between the two groups (mean ± SD)

Index	Research group (n = 44)	Control group (n = 44)	t value	P value
AFU (U/L)				

Preoperative	66.41 ± 9.51	68.18 ± 10.84	-0.814	0.418
1 mo after operation	27.04 ± 6.44 ^a	29.95 ± 8.27 ^a	-1.842	0.069
AFP (ng/L)				
Preoperative	240.8 ± 75.6	228.6 ± 66.3	0.805	0.423
1 mo after operation	78.55 ± 18.04 ^a	82.01 ± 20.63 ^a	-0.837	0.405
CEA (µg/L)				
Preoperative	18.58 ± 4.20	20.03 ± 4.81	-1.506	0.136
1 mo after operation	3.77 ± 0.89 ^a	4.01 ± 0.81 ^a	-1.323	0.189

^a*P* < 0.05 *vs* this group before surgery.

AFU: Alpha-L fasyolase; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen.

Table 5 Comparison of inflammatory factors between the two groups of patients before and after surgery (mean ± SD)

Index	Research group (<i>n</i> = 44)	Control group (<i>n</i> = 44)	<i>t</i> value	<i>P</i> value
IL-6 (pg/mL)				
Preoperative	54.23 ± 9.50	56.39 ± 9.11	-1.089	0.279
24 h after operation	97.41 ± 17.59	108.26 ± 18.25	-2.839	0.006
72 h after operation	70.55 ± 13.02	74.18 ± 14.40	-1.240	0.218
TNF-α (pg/mL)				
Preoperative	68.33 ± 13.20	70.53 ± 12.65	-0.798	0.427
24 h after operation	148.12 ± 21.04	167.00 ± 24.28	-3.898	0.000
72 h after operation	98.40 ± 13.27	102.73 ± 15.19	-1.424	0.158
CRP (mg/L)				
Preoperative	4.91 ± 1.53	5.34 ± 1.58	-1.297	0.198
24 h after operation	18.48 ± 3.75	20.14 ± 4.43	-1.897	0.061
72 h after operation	14.20 ± 3.36	15.38 ± 4.28	-1.438	0.154

IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein.

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