

Perioperative Antiviral Treatment Facilitate the Postoperative Recovery for Patients with HBV Related to Hepatocellular Carcinoma

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Abstract Objective: This study aimed to determine whether perioperative antiviral treatment is facilitate for patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) and Child-Pugh grade A cirrhosis in perioperative recovery of liver function and HBV activation. **Methods:** The study included 115 patients with HBV-related HCC and Child-Pugh grade A cirrhosis who underwent resection. Patients were prospectively assigned to a preoperative antiviral treatment group (n = 51) or postoperative antiviral treatment group (n = 52); twelve patients who had not received antiviral treatment before and after surgery were designated a non-treatment group (n = 12). HBV reactivation during a month after the operation was defined as a HBV DNA value tenfold over preoperative values. Postoperative liver dysfunction was defined as prothrombin activity <50% and serum bilirubin >50 mmol/L on postoperative day 5. **Results:** Postoperatively, liver dysfunction was present in 1 of 51 (1.96%) patients who received preoperative antiviral therapy, 1 of 52 (1.92%) who received postoperative therapy, and 3 of 12 (25%) who received no antiviral therapy. HBV reactivation postoperatively occurred at similar rates. **Conclusions:** Preoperative and postoperative antiviral treatment of patients with Child-Pugh grade A cirrhosis and high levels of HBV DNA undergoing hepatic resection for HCC are both facilitate in preventing perioperative liver dysfunction and reactivation of HBV. Thus, in this population with high levels of HBV DNA, perioperative antiviral treatment is important.

Keywords: HBV-related hepatocellular carcinoma; Hepatectomy; Antiviral treatment; Perioperative antiviral treatment

1. Introduction

Hepatitis B virus (HBV) can be activated after hepatectomy.[1-10] HBV reactivation influences postoperative recovery of liver function, the recurrence of liver cancer, and long-term survival after hepatectomy. [1-10] Perioperative antiviral treatment can reduce HBV reactivation, postoperative liver dysfunction, and recurrence of liver cancer, thereby improving long-term survival after resection for HBV-related hepatocellular carcinoma (HCC).[11-15] However, most of the studies of patients undergoing surgical treatment for HBV-related HCC have assessed antiviral therapy given after resection; few have assessed therapy given before resection. [16] And preoperative antiviral therapy is recommended for HBV carriers who will receive partial hepatectomy. [17] This study compared the relative perioperative effectiveness of

preoperative and postoperative antiviral treatment of patients with Child-Pugh grade A cirrhosis undergoing hepatic resection of HBV-related HCC; some patients who declined antiviral therapy also were evaluated.

2. Patients and Methods

2.1. Study design

This study included 115 patients with HBV-related HCC and Child-Pugh grade A cirrhosis who underwent liver resection at the Affiliated Hospital of Guilin Medical University, Guangxi, China, between January 2014 and July 2016. Patients who received perioperative antiviral treatment were prospectively assigned alternately to one of two groups according to the sequence of admission to the hospital: preoperative antiviral treatment group ($n = 51$) and postoperative antiviral treatment group ($n = 52$). In the same period, 12 patients did not receive perioperative antiviral treatment and were designated the non-antiviral treatment group ($n = 12$). All patients' preoperative HBV DNA values were higher than 2000 IU/ml. Patients in the preoperative treatment group received orally administrated Entecavir (Dawnrays Pharmaceutical Co., LTD, Jiangsu, China) 0.5 mg once a day during the first 3 days before operation and until the day of operation; after operation, the drug was given via gastric tube until the tube was removed (usually on postoperative day 3). Patients in the postoperative treatment group began receiving Entecavir (0.5 mg/d) orally after the gastric tube was removed. The study mainly evaluated recovery of liver function and rate of HBV reactivation during 1 week and 1 month after surgery, respectively.

2.2. Patients

A total of 115 patients with HBV-related HCC who underwent liver resection were enrolled in the study, which was approved by The Clinical Research Ethics Committee of the Affiliated Hospital of Guilin Medical University. All assigned patients were given conventional perioperative prophylaxis antibiotic drugs, gastric-acid inhibitor drugs, and nutritional support. Resected liver tissues were examined histologically.

The criteria for inclusion in the study were these: 1) the primary liver cancer was confirmed by preoperative clinical diagnosis; 2) HBV surface antigen was positive; 3) the patient had not received antiviral treatment before admission into this hospital; 4) the patient's condition was satisfactory for major surgery; 5) the preoperative liver function was Child-Pugh grade A. The exclusion criteria were these: 1) metastatic or recurrent liver cancer confirmed by postoperative pathologic examination; 2) concurrent hepatitis C virus or HIV; 3) serious cardiac, pulmonary or renal disease; 4) patient had received transarterial chemoembolization or other antitumor therapies before operation; 5) preoperative aspartate aminotransferase and/or alanine aminotransferase >100 U/L; and 6) pregnant or lactating women.

2.3. Clinical diagnosis and definitions

The cut-off of HBV DNA value for grouping was in accordance with Asian Pacific guidelines.[18] HBV reactivation during a month after the operation was defined as postoperative HBV DNA level increased tenfold over preoperative values. The diagnosis of HCC was confirmed by histopathological examination. Postoperative liver dysfunction was defined as prothrombin activity $<50\%$ and serum bilirubin >50 mmol/L on postoperative day 5.[19]

2.4. Surgical methods

The operations were conducted by surgeons skilled in liver resection. The selection of the surgical method was based on the results of operative exploration, preoperative examination, relevant indicators (preoperative indocyanine green retention rate at 15 minutes and Child-Pugh classification), and the size and location of the tumor. All patients were given intravenous anesthesia. The methods of liver resection ($n = 115$) were these: nonanatomic liver resection or local tumor resection ($n = 46$), left hemihepatectomy ($n = 22$), right hemihepatectomy ($n = 14$), caudate lobe resection ($n = 11$), mesohepatectomy ($n = 10$), and left lateral liver resection ($n = 14$). The number of minor and major hepatectomy were 29 and 22 in preoperative

antiviral treatment group, 33 and 19 in postoperative antiviral treatment group, and 7 and 5 in non-treatment group, respectively.

2.5. Biochemical tests

Blood tests on the patients were performed after fasting overnight on the second morning after hospital admission. Biochemical test results were reviewed on the first, third, fifth, seventh, tenth, and fifteenth day after operation. Subsequently, blood tests were conducted once every month. Blood tests included routine blood, liver function, blood coagulation function, HBV DNA, and five indices of hepatitis b infection (hepatitis B surface antigen; antibody to hepatitis B surface antigen; hepatitis B e antigen; antibody to hepatitis B e antigen; and antibody to hepatitis B core antigen). Serum HBV DNA concentration was determined with polymerase chain reaction.

2.6. Statistical analysis

Normally distributed variables were presented as mean \pm standard deviation and compared by the t-test. Classification variables were compared by use of chi-squared tests. All analyses were performed with the SPSS 19.0 software for windows (SPSS Inc., IL, USA). $P < 0.05$ was considered statistically significant.

3. Results

Table 1. Comparison of clinical indexes among three patient groups

Index	Pre-group (n=51)	Post-group (n=52)	Non-group (n=12)	t ₁ Value	P ₁ Value	t ₂ Value	P ₂ Value	t ₃ Value	P ₃ Value
Age (years)	50.85 \pm 10.63	49.36 \pm 11.46	44.92 \pm 13.88	0.616	0.539	1.585	0.119	-1.129	0.264
Sex (Female/Male)	8/43	6/46	4/8		0.539		0.161		0.061
Preoperative HBV DNA (log)	4.55 \pm 1.08	4.51 \pm 1.16	4.97 \pm 1.09	-0.139	0.890	1.23	0.224	1.23	0.224
Diameter of tumor (cm)	6.32 \pm 4.083	6.65 \pm 4.45	6.10 \pm 3.21	-0.314	0.754	-1.57	0.876	-3.359	0.721
INR	1.02 \pm 0.07	1.03 \pm 0.09	1.04 \pm 0.12	-0.926	0.357	-0.314	0.628	0.175	0.862
Total bilirubin (umol/L)	13.52 \pm 4.68	13.64 \pm 5.24	11.91 \pm 5.58	-0.111	0.912	1.00	0.321	-0.993	0.325
Albumin (g/L)	38.57 \pm 3.56	36.92 \pm 4.73	37.60 \pm 4.77	1.845	0.069	-0.766	0.447	0.455	0.651
AST (U/L)	39.78 \pm 15.32	43.19 \pm 21.87	41.09 \pm 12.96	-0.822	0.413	0.217	0.787	-0.315	0.754
ALT (U/L)	37.87 \pm 19.31	33.41 \pm 19.64	33.53 \pm 10.85	1.043	0.300	-0.213	0.833	0.894	0.376
type of hepatectomy(Min or/Major)	29//22	33/19	7/5		0.496		0.927		0.743
Liver dysfunction	3	3	3		0.980		0.042		0.039
HBV reactivation	1	1	3		0.989		0.031		0.014

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus; INR: international normalized ratio; Pre-group refers to patient who received antiviral treatment before operation; Post-group refers to patients who received antiviral treatment immediately after operation; Non-group refers to patients who did not receive antiviral treatment; t₁ and P₁ were the comparison between groups Pre-group and Post-group, t₂ and P₂ between groups Pre-group and Non-group, and t₃ and P₃ between groups Post-group and Non-group.

The clinical indexes of the three groups of patients are presented in Table 1. No differences were found in age, sex and preoperative values of HBV DNA concentrations, tumor diameter, international normalized ratio, total serum bilirubin, aspartate aminotransferasealanine aminotransferase and types of hepatectomy among the groups. Postoperatively, significant differences between the groups were recorded: Liver dysfunction was present in 1 of 51 (1.96%) patients who

received preoperative antiviral therapy and 1 of 52 (1.92%) who received postoperative therapy. In contrast, 3 of 12 patients (25%) who received no antiviral therapy had liver dysfunction. HBV reactivation postoperatively also occurred significantly less frequently in patients who received preoperative antiviral therapy (1/51; 1.96%) or postoperative therapy (1/52; 1.92%) than in those who received no antiviral therapy (3/12; 25%).

4. Discussion

4.1. Perioperative antiviral treatment

The present study found that patients who did not receive antiviral treatment had a much higher rate of postoperative HBV reactivation and a lower rate of postoperative recovery of liver function than did patients who received either preoperative or postoperative antiviral treatment. In several studies, [1,5,20-22] the rate of postoperative HBV reactivation was 14%–33% in patients who did not receive perioperative antiviral treatment. Related studies [1,20,22] have found the rate of postoperative HBV reactivation to be 1.4%–2.9% in patients with perioperative antiviral treatment. Both of these results are similar to the results in our study. However, none of the reported studies [9,12,14,20-22] directly compared the incidence of HBV reactivation or recovery of liver function in patients who received preoperative antiviral treatment with the incidence in those who received postoperative treatment; this comparison is a unique and important feature of our study.

HBV, if activated, significantly impedes the recovery of liver function, increases the rate of postoperative tumor recurrence and reduces the survival rate. [21-24] Perioperative antiviral treatment can reduce postoperative liver damage and the recurrence of postoperative tumor, and can promote the recovery of liver function and improve postoperative survival. [11-13,23,24] Antiviral treatment can significantly decrease the reactivation of HBV in patients with HBV-related HCC undergoing liver resection. [1,4-10,15,21] Some authors [1,5,21] have reported a high rate of HBV reactivation and a high chance of liver failure in patients who had low preoperative HBV DNA values and did not receive perioperative antiviral treatment after liver resection. The preoperative positive serum HBV-DNA may have activated HBV after the liver resection, and preoperative undetectable HBV DNA did not seem to assure nonreplicating HBV after surgery; [21] perioperative antiviral treatment was the only factor that prevented the HBV reactivation [21].

4.2. Preoperative antiviral treatment

In this study, no significant difference was found in the postoperative recovery of liver function and the rate of postoperative HBV reactivation between preoperative and postoperative antiviral treatment. Zhang, et al [4] reported that 72 patients with HBV DNA $>10^4$ IU/ml received antiviral treatment with Entecavir tablets before hepatectomy; surgery was delayed until the HBV-DNA was less than 10^4 IU/ml, and patients continued to use the antiviral drugs after surgery. Forty patients with HBV DNA $>10^4$ IU/ml in the control group did not receive antiviral treatment before or after surgery. An absence of hepatitis B recrudescence and faster recovery of postoperative liver function indices were observed in the antiviral treatment group. Similar to our experience, preoperative antiviral treatment was similar to postoperative antiviral treatment for patients with preoperative high HBV DNA level and Child-Pugh grade A [12]. Preoperative antiviral treatment is beneficial to the patient, and it is necessary for these patients to start preoperative antiviral treatment before surgery. But a long time is required to control the virus, and the preoperative preparation time for patients diagnosed with HBV-related HCC for the first time is limited, usually 3–7 days. It is unclear whether it is necessary for these patients HBV DNA must be reduced to a certain level before surgery. Thus, This doubt needs further research.

5. Conclusions

Preoperative and postoperative antiviral treatment of patients with Child-Pugh grade A cirrhosis and high levels of HBV DNA undergoing hepatic resection for hepatocellular carcinoma resulted in similarly low rates (about 2%) of postoperative liver dysfunction and reactivation of HBV. In contrast, patients who did not receive perioperative antiviral treatment had higher rates (about 25%) of postoperative liver dysfunction and reactivation of HBV. Thus, in patients with high levels of HBV DNA, perioperative antiviral treatment is important.

6. Limitations of This Research

The study included a relatively small number of cases, from a single research center. Long-term survival and tumor recurrence were not evaluated. The study also did not have a completely randomized design. Finally, the study's results need to be validated in multicenter, prospective, randomized studies with larger numbers of patients.

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8. Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

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