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Original Article

Factors associated with postoperative HBV reactivation in HBV related hepatocellular carcinoma patients with HBV-DNA levels less than the minimum

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Abstract: Objective: This study was aim to clarify the postoperative hepatitis B virus reactivation (PHR) and risk factors of PHR in hepatocellular carcinoma (HCC) patients with hepatitis B virus (HBV)-DNA levels less than the minimum. And to figure out the significance of antiviral therapy on liver function recovery after hepatectomy. Methods: A total of 74 HCC patients with preoperative HBV-DNA levels less than minimum were analyzed. Patients were divided into 2 groups, 20 HCC patients were given antiviral therapy at least 3 days before hepatectomy, and 54 HCC patients were not given antiviral therapy. Results: Of the 74 HCC patients enrolled, 16 (21.6%) HCC patients suffered PHR. Among non-antiviral group, 15 (27.0%, 15/54) patients suffered PHR. While for antiviral therapy group, only 1 (5.0%, 1/20) patient suffered PHR. The difference was statistically significant. Patients in antiviral group had a faster recovery of albumin. Conclusion: HCC patients with HBV-DNA levels less than minimum still has the risk of PHR. Preoperative antiviral therapy could significantly decrease the incidence of PHR, which may also improve postoperative liver function.

Keywords: Hepatocellular carcinoma, hepatitis B virus, postoperative HBV reactivation, antiviral therapy, hepatectomy

Introduction

Primary liver cancer is one of the most common cancers in China, and 90% of primary liver cancer is hepatocellular carcinoma (HCC). Now the preferred method of HCC is still surgery, but HCC recurrence within 5 years is up to 50%-70% [1, 2].

Continuous high hepatitis B virus (HBV) DNA level is an important factor of HCC recurrence and postoperative HBV reactivation (PHR) is an independent risk factor for HCC recurrence [3]. After liver resection, PHR occurs in patients with detectable HBV-DNA levels, and antiviral therapy can effectively reduce PHR rate [4]. Therefore, antiviral therapy is recommended to patients with detectable HBV-DNA levels [5]. However, PHR in preoperative HBV-DNA negative HCC patients cannot be ignored [6]. Whether preoperative antiviral therapy is necessary for HBV-DNA negative HCC patients remains inconclusive in international guidelines [7, 8].

Therefore, we adopted a prospective study to explore PHR and its influence factor in HCC patients with HBV-DNA levels less than minimum standard. And to further explore the effect of antiviral therapy in the inhibition of PHR and the impact on perioperative liver function.

Patients and methods

General information

A total of 74 HCC patients (64 males and 10 females) in Affiliated Tumor Hospital of Guangxi Medical University from July 2013 to December 2014 were included for the prospective study. All HCC were confirmed by pathology, and were consistent with clinical diagnostic criteria. HCC

Table 1. Baseline charateristic of HCC patients with HBV-DNA levels less than minimum

Index	With antiviral therapy (n=20)	Without antiviral therapy (n=54)	P
Sex (M/F)	17/3	47/7	0.823
Age (years)	50±10	49±12	0.877
HBsAg, μg/L	261.0±182.4	188.6±153.6	0.156
AFP, (μg/L)	2136 (1.77, 12100)	2458 (0.8, 12100)	0.513
Operating time, (min)	204.7±62.9	190.9±53.6	0.606
Liver cirrhosis			
Less than light, n (%)	12 (60%)	39 (72.3%)	0.320
More than moderate, n (%)	8 (40%)	15 (27.7%)	
Blood loss, (ml)	392.5±235.2	355.5±267.8	0.937
Blood transfusion			
No, n (%)	17 (85%)	44 (81.5%)	0.728
Yes, n (%)	3 (15%)	10 (18.5%)	
Tumor diameters, (cm)	7.2±5.6	6.4±3.2	0.895
Tumor number			
=1, n (%)	17 (85%)	39 (72.3%)	0.219
>1, n (%)	3 (15%)	15 (27.7%)	
Surgical resection			
<1 cm, n (%)	10 (68.8%)	24 (44.4%)	0.657
≥1 cm, n (%)	10 (31.2%)	30 (55.6%)	
BCLC stage			
Stage A, n (%)	15 (75%)	28 (51.8%)	0.192
Stage B, n (%)	1 (5%)	12 (22.2%)	
Stage C, n (%)	4 (10%)	14 (26%)	
PVTT			
No, n (%)	16 (90%)	40 (74.1%)	0.604
Yes, n (%)	4 (10%)	14 (25.9%)	
PHR			
No, n (%)	19 (95%)	39 (62.3%)	0.005
Yes, n (%)	1 (5%)	15 (27.7%)	

patients should be HBV infected (HBV surface antigen positive, HBsAg) and with undetectable HBV-DNA levels.

Perioperative management

Before surgery, each patient was extracted peripheral venous blood for liver function detection in the fasting state, including: total bilirubin (TBil), direct bilirubin (DBil), total protein (TP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), PT, and HBV-DNA load.

HBV-DNA levels

HBV-DNA minimum detection value was 500 IU/ml. After the first three days and seven days, each patient was extracted 3 ml peripheral venous blood for liver function retest, and 2 ml for HBV-DNA load retest.

Antiviral therapy

Antiviral group started preoperative antiviral therapy three days before surgery, and continued postoperative antiviral therapy after recovery of eating. For non-antiviral group, no antiviral drugs were provided. Entecavir dispersible tablets (Runzhong, CHIA TAI TIANQING Company, Jiangsu, China) were selected as antiviral therapy, 0.5 mg/time, once per day.

Postoperative HBV reactivation

PHR index was set as HBV-DNA >500 IU/ml [9]. Postoperative HBV-DNA negative (HBV-DNA <500 IU/ml) meant inactivation.

Postoperative liver function

The first 3-day liver function difference: we used the liver function levels on postoperative day (POD) 3 to subtract preoperative liver function levels. And, the first 7-day liver function difference: we used the liver function levels on POD 7 to subtract preoperative liver function levels. Moreover, we compared these 2 differences between PHR subgroups and also in antiviral subgroups to investigate which subgroup and recover faster from the surgery.

Statistical analysis

Statistical program for social sciences (SPSS) software package version 20.0 (Chicago, IL, USA) was used to perform all the statistical analyses. $P<0.05$ represented difference was statistically significant. Normally distributed data were expressed as mean ± standard deviation (SD), while asymmetrically distributed

Table 2. The difference between preoperative liver function level and liver function level on POD 3, 7 in patients with or without PHR

Index	PHR (Baseline)	Non-PHR (Baseline)	P	PHR (POD 3)	Non-PHR (POD 3)	P	PHR (POD 7)	Non-PHR (POD 7)	P
TBIL (μmol/L)	11.78±5.23	10.62±4.97	0.876	9.90 (1.90-14.90)	8.25 (4.27-15.07)	0.642	14.05 (7.57-17.15)	10.00 (8.05-13.40)	0.341
DBIL (μmol/L)	5.64±2.13	5.51±2.07	0.965	6.10 (1.60-9.37)	5.90 (2.87-9.42)	0.871	1.15 (-0.30-4.07)	2.95 (0.30-5.62)	0.502
TP (g/L)	69.71±9.46	68.46±8.76	0.864	15.20 (12.60-23.10)	14.90 (9.10-19.85)	0.409	13.20 (6.17-21.60)	10.00 (5.37-14.25)	0.19
ALB (g/L)	39.76±4.62	41.76±4.76	0.435	10.00 (7.27-13.52)	8.60 (6.17-11.75)	0.150	11.75 (8.35-15.04)	8.20 (4.47-10.45)	0.016*
ALT (U/L)	65.70 (29.60-100.97)	42.10 (26.10-89.40)	0.834	274.50 (153.50-513.00)	219.50 (102.50-333.25)	0.237	57.50 (38.25-92.5)	43.00 (14.0-81.25)	0.048*
AST (U/L)	60.80 (25.70-120.00)	48.20 (22.80-85.50)	0.907	117.50 (81.75-277.25)	108.00 (54.00-138.00)	0.989	7.00 (0.00-28.7)	2.00 (-10.5-8.75)	0.678
PT (s)	12.55±0.90	12.74±1.21	0.983	1.75 (0.92-2.97)	1.95 (1.00-3.12)	0.570	0.65 (-0.75-2.27)	1.10 (0.50-2.00)	0.383

Note: *P<0.05.

Table 3. The difference between preoperative liver function level and liver function level on POD 3, 7 in patients with or without antiviral therapy

Index	Antiviral group (Baseline)	Non-antiviral group (Baseline)	P	Antiviral group (POD 3)	Non-antiviral group (POD 3)	P	Antiviral group (POD 7)	Non-antiviral group (POD 7)	P
TBIL (μmol/L)	10.65±4.74	12.92±8.5	0.263	10.15 (4.05-18.07)	7.90 (3.50-13.50)	0.527	9.05 (7.22-13.80)	11.25 (8.27-14.70)	0.263
DBIL (μmol/L)	5.15±2.08	5.63±3.02	0.517	7.40 (2.10-11.30)	5.50 (2.57-9.15)	0.695	3.6 0 (0.77-5.87)	1.90 (-0.07-4.60)	0.529
TP (g/L)	68.97±8.66	70.31±9.68	0.588	15.95 (5.87-18.95)	14.3 0 (10.40-21.00)	0.203	10.25 (1.40-13.87)	10.60 (5.95-16.80)	0.117
ALB (g/L)	39.95±4.39	42.72±4.78	0.027	8.10 (3.85-10.90)	8.85 (6.57-13.17)	0.035	6.80 (3.22-10.75)	9.00 (5.95-12.57)	0.043*
ALT (U/L)	60.20 (30.60-100.10)	45.10 (25.20 -90.20)	0.295	229.00 (107.75-317.50)	243.00 (117.75-362.50)	0.750	65.50 (25.25-88.50)	44.00 (13.75-83.50)	0.924
AST (U/L)	61.15 (31.20-108.70)	42.60 (22.40-92.30)	0.435	108.00 (56.75-135.00)	112.00 (59.70-174.25)	0.652	3.50 (-7.75-11.00)	2.00 (-15.25-12.50)	0.572
PT (s)	12.65±0.95	12.73±1.46	0.085	2.35 (0.77-3.10)	1.80 (1.00-3.05)	0.327	0.95 (0.52-1.52)	1.10 (0.27-2.00)	0.841

Note: *P<0.05.

data were expressed as median (range). The group comparison between ranked data was applied by Mann-Whitney U test; comparison of categorical variable rate was applied by χ^2 test. Firstly univariate logistic regression was used to identify risk factors associated with activation. Afterwards, multivariate analysis was used to examine significant univariate factors by a stepwise logistic model.

Results

Characteristics of the study population

A total of 74 HCC patients with HBV-DNA levels less than minimum were prospective included in our study. Patients were divided into 2 groups, 20 patients were antiviral therapy group, and other 54 patients were non-antiviral therapy. The baseline characters were similar between two groups (**Table 1**).

Postoperative HBV reactivation

For the whole group of patients, PHR rate was 21.6% (16/74), PHR rate of non-antiviral group was 27.7% (15/54), and PHR rate of antiviral group was 5.0% (1/20). The difference of PHR rate between the two groups was statistically significant (P<0.05).

We conducted multivariate regression analysis and found 12 factors were associated with PHR. Age over 40 years old [odds ratio (OR)=0.277, *P*<0.001], AFP more than 400 μg/L (OR=0.200, *P*<0.001), irregular resections (OR=0.300, *P*<0.001), operating time more than 180 minutes (OR=0.233, *P*=0.001), hepatic occlusion more than 20 minutes (OR=0.320, *P*=0.005), moderate to high level of liver cirrhosis (OR=0.278, *P*=0.011), blood loss more than 500 ml (OR=0.188, *P*=0.008), tumor larger than 5 cm, (OR=0.289, *P*<0.001), incomplete capsule (OR=0.273, *P*=0.005), surgical margin less than 1 cm (OR=0.143, *P*<0.001), the presence of portal vein tumor thrombus (OR=0.200, *P*=0.011) and no antiviral therapy (OR=0.053, *P*=0.004) were risk factors associated with PHR. All these 12 factors were examined by multivariate analysis and found preoperative non-antiviral therapy [OR=13.95, 95% confidence interval (CI) 1.358 to 143.379, P=0.027] were the independent risk factors for HBV reactivation.

Postoperative liver function difference between patients with or without PHR

For the first 3-day liver function difference, we used the liver function on POD 3 to subtract preoperative level, and found that liver function changes were similar between patients with or without PHR (*P*>0.05). For the first 7-day liver function difference, we used the liver function on POD 7 to subtract preoperative level, and found that the recovery of ALB (*P*=0.016) and ALT (*P*=0.048) in patients with PHR were slower than in patients without PHR (**Table 2**).

Postoperative liver function difference between patients with or without antiviral therapy

For the first 3-day liver function difference, we used the liver function on POD 3 to subtract preoperative level, and found that liver function changes were similar between patients with or without antiviral therapy (*P*>0.05). For the first 7-day liver function difference, we used the liver function on POD 7 to subtract preoperative level, and found that ALB in patients with antiviral therapy was recovered faster than patients without antiviral therapy (**Table 3**).

Discussion

In recent years, with the surgical idea changes and surgical equipment updates, the prognosis of HCC patients has been improved, but high recurrence rate of HCC still remains a major problem to hepatobiliary surgeons. Studies have shown that HBV reactivation is easily occurred in chemotherapy, immunosuppressive therapy, radiation therapy [10], hepatic arterial chemoembolization, radiofrequency ablation, hepatic resection, and liver transplantation process [11] in HBV-related HCC patients. Whether liver resection can lead to PHR in HBV-related HCC patients has formed wide attention.

In this study, a total of 74 HCC patients with HBV-DNA levels less than minimum were included, all patients were underwent liver resection. PHR occurred in 16 patients, among them, the PHR rate of non-antiviral group and antiviral group was 27% (15/54) and 5.0% (1/20) respectively, the difference was with statistical significance. Whether preoperative antiviral therapy is necessary, experts recommend that HBV related HCC patients with HBV-DNA posi-

tive, NAs antiviral treatment should be given. For HBV-related HCC patients with HBV-DNA negative, PHR and HBV-DNA should be closely monitored when receiving transcatheter arterial chemoembolization, radiation therapy or chemotherapy [12].

Surgery can lead to PHR, however, PHR is the result of multiple factors. We further explored the pathologic factors on PHR and found that portal vein occlusion, liver cirrhosis, blood loss, surgical approach and other indicators are irrelevant to PHR. Multivariate analysis showed that non-antiviral therapy is probably an independent risk factor for PHR.

HBV reactivation will increase liver dysfunction and risk of liver failure [13], which will affect postoperative liver function recovery, increase recurrence rate, and shorten the survival rate. In recent years, perioperative antiviral therapy is being valued. Entecavir has become the guidelines recommend medication due to its fast and potent antiviral activity [14], a number of studies have shown that preoperative entecavir can effectively prevent PHR, improve liver function, reduce tumor recurrence and prolong survival rate [15].

In this study, we found that the difference of 3-day postoperative liver function of the two groups was not significant; the difference of 7-day postoperative ALB (P=0.016) and ALT (P=0.048) values was statistically significant. The recovery of ALB and ALT in activation group was slower than inactivation group. We considered that the changes of ALT in 3 days postoperative are mainly related to surgery. The administration of exogenous human albumin and supportive treatment within 3 days postoperative will affect the statistical results. PHR will influence ALB and ALT recovery. The 7-day postoperative ALB value was significantly different in antiviral group and non-antiviral group (P=0.043). The postoperative ALB will recover more rapidly in antiviral group, postoperative antiviral therapy can increase liver function recovery.

In conclusion, HCC patients with HBV-DNA levels less than minimum were also able to occur PHR. Preoperative antiviral therapy is necessary, non-antiviral therapy may be an independent risk factor for PHR. Entecavir can effectively inhibit postoperative HBV reactivation and accelerate the recovery of liver function.

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Disclosure of conflict of interest

None.

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