·临床研究与应用·

术前抗病毒治疗对HBV-DNA阴性肝细胞癌患者术后病毒再激活及肝功能的影响*

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摘要 **目的**：评估术前抗病毒治疗对术后乙肝病毒再激活以及肝功能的影响。**方法**：2012年7月至2016年3月将广西医科大学附属肿瘤医院肝胆胰脾外科乙肝病毒DNA阴性的HCC患者分成抗病毒组(66例)及对照组(108例)，抗病毒组术前给予恩替卡韦分散片抗病毒治疗，对照组未给予抗病毒治疗。统计分析术后HBV再激活及肝功能指标变化情况。**结果**：抗病毒组HBV激活率为3%(2/66)，对照组为27.8%(30/108)。多因素分析显示小部分肝切术(HR=4.695；95% CI：1.257-17.537，*P*=0.021)及术前未抗病毒治疗(HR=8.164；95% CI：1.831-36.397，*P*=0.006)是术后HBV再激活的危险因素。抗病毒组与未抗病毒组，激活组与未激活组术后7天内肝功能指标差异无统计学意义(*P*>0.05)，术后30天比较，ALT及ALB差异有统计学意义(*P*<0.05)。**结论**：对于DNA阴性的HCC患者，肝切除术可导致HBV再激活，术前抗病毒治疗能有效降低HBV再激活风险及保护肝功能。

关键词 HBV-DNA 肝细胞癌 再激活 抗病毒治疗 肝切除术
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Influence of preoperative antiviral therapy on HBV reactivation and liver function after liver resection in HBV-DNA-negative hepatocellular carcinoma patients

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Abstract **Objective:** To evaluate the effect of antiviral therapy on HBV reactivation and liver function after liver resection in patients with hepatocellular carcinoma (HCC). **Methods:** A total of 174 HBV-DNA(-) HCC patients were recruited into two groups: antiviral therapy group (66 cases) and control group (108 cases). In the antiviral group, patients were given entecavir dispersible tablet, whereas no antiviral therapies were given in the control group. The HBV reactivation and liver function index rates were statistically analyzed. **Results:** Rates of HBV reactivation after hepatectomy were 3.0% and 27.8% in the antiviral therapy group and control group, respectively. Multivariate analysis revealed that minor hepatectomy (*HR*, 4.695; 95% *CI*, 1.257-17.537, *P*=0.021) and no antiviral therapy (*HR*, 8.164; 95%*CI*, 1.831-36.397, *P*=0.006) were independent risk factors for HBV reactivation. The levels of ALT, TBil, ALB, and PT within 7 days after liver resection were similar between the antiviral therapy group and the control group and between the reactivation group and no-reactivation group. However, the ALT and ALB levels were significantly better in the antiviral group compared with that in the control group after 30 days. **Conclusion:** HBV reactivation can occur after liver resection for HBV-DNA(-) HCC patients. Preoperative antiviral therapy can reduce the risk of HBV reactivation, thus protecting liver function in patients undergoing liver resection.

Keywords: HBV-DNA, hepatocellular carcinoma, reactivation, antiviral therapy, liver resection

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乙型肝炎病毒(hepatitis B virus,HBV)感染是肝细胞性肝癌(hepatocellular carcinoma,HCC)最主要的致病因素,我国95%以上的HCC患者合并HBV感染[1]。肝切除术是治疗HCC的首选方法,然而术后高病毒激活率及复发率仍是最大难题。国内外文献证实HBV-DNA高载量是HCC术后复发的主要原因,术后HBV再激活是术后肿瘤复发的独立危险因素[2],为了降低术后再激活及降低肿瘤复发,HBV相关性HCC患者抗病毒治疗日益受到重视。

抗病毒治疗能有效控制肝炎活动、保护肝功能、降低肿瘤复发、为肿瘤复发的后续治疗提供机会以及改善HCC患者预后等[3]。国内外抗病毒指南及专家共识[4-7]指出:HBV-DNA阳性的HCC患者给予肝切除术、肝动脉化疗栓塞等抗肿瘤治疗期间可导致HBV再激活,从而增加了肿瘤复发风险,导致肝功能损害,影响患者预后。因此术前应联合强效高耐药屏障核苷酸类药物[8]抗病毒治疗。

对于HBV-DNA阴性的HCC患者在接受肝切除术前是否需要抗病毒治疗目前仍缺乏高级别证据。本研究拟以HBV-DNA阴性的HCC手术患者为研究对象,前瞻性观察术后HBV再激活率以及抗病毒治疗对肝功能的影响,旨在为HBV-DNA阴性的HCC患者在接受手术前是否需要抗病毒治疗提供可靠的临床依据。

1 材料与方法

1.1 一般资料

2012年7月至2016年3月收集广西医科大学附属肿瘤医院肝胆胰脾外科首次行肝切除术的HBV阳性HCC患者174例,其中男性150例、女性24例;年龄24~72岁。纳入标准:1)乙肝表面抗原(HBsAg)阳性;2)HBV-DNA阴性;3)谷丙转氨酶(alanine aminotransferase,ALT)正常;4)肝功能Child-Pugh分级A级;5)术后病理证实HCC。排除标准:1)术前给予TACE和或其他抗肿瘤治疗;2)近1年有抗病毒治疗史;3)合并免疫代谢性疾病、其他肿瘤或严重疾病者。本研究经医院伦理道德委员会批准,在签署知情同意的情况下将患者分成抗病毒组及对照组。

1.2 方法

1.2.1 围手术期管理 抗病毒组术前3天给予恩替卡韦分散片(entecavir,ENT)0.5 mg/d抗病毒治疗直至术后至少1个月。对照组未给予任何抗病毒治疗,如术后HBV激活且符合抗病毒标准则给予抗病毒治疗。所有患者术前检测乙肝两对半、丙肝抗体、转氨酶、肝功能、凝血功能、HBV-DNA、肝脏增强CT、甲胎蛋白等。术中记录手术方式、出血量、输血量、肿瘤大小、包膜情况、手术时间等。术后1,3,5,7,30天各复查肝功能、凝血功能、HBV-DNA。两组患者围手术期未接受任何的免疫治疗。

1.2.2 HBV术后再激活标准[9-11] 术前HBV-DNA阴性,术后HBV-DNA阳性,则定义为HBV再激活。

1.3 统计学分析

应用SPSS 17.0软件处理数据,连续变量以$\bar{x}\pm s$表示,t检验进行分析;计数资料采用百分比表示,χ^2或Fisher's检验进行分析,采用logistic回归分析进行多因素分析。P<0.05为差异具有统计学意义。

2 结果

2.1 临床资料比较

共66例HBV-DNA阴性的HCC患者接受抗病毒治疗,108例HCC未接受抗病毒治疗,两组术前白蛋白比较(40.24±5.19 *vs*. 42.57±4.61,P=0.032),差异具有统计学意义。两组切肝量比较(P=0.041)差异具有统计学意义。两组临床数据比较见表1。

2.2 HBV激活率比较

HBV分别于术后d1激活8例,d3激活16例,d5激活5例,d7激活2例,d9激活1例,d30激活0例。抗病毒组HBV激活率3.0%(2/64),未抗病毒组HBV激活率27.8%(30/108),差异具有统计学意义(P<0.001)。

单因素分析,术前存在肝硬化、白蛋白、小部分肝切术以及未抗病毒治疗是HBV激活的风险因素(表2);采用logistic回归多因素分析,小部分肝切术及未抗病毒治疗是HBV激活的风险因素(表3)。

2.3 HBV激活对肝功能的影响

术后d3,d5,d7,抗病毒组及对照组在ALT、TBil、ALB、PT方面比较差异均无统计学意义(P>0.05)。术后30天比较,ALT及ALB比较,差异有统计学意义(P<0.05,图1)。

术后d3,d5,d7,HBV激活组及未激活组在ALT、TBil、ALB、PT方面比较。差异均无统计学意义(P>0.05)。术后30天比较,ALT及ALB比较,差异有统计学意义(P<0.05,图2)。

表1 患者一般临床特征

Table 1 Baseline characteristics of all included patients

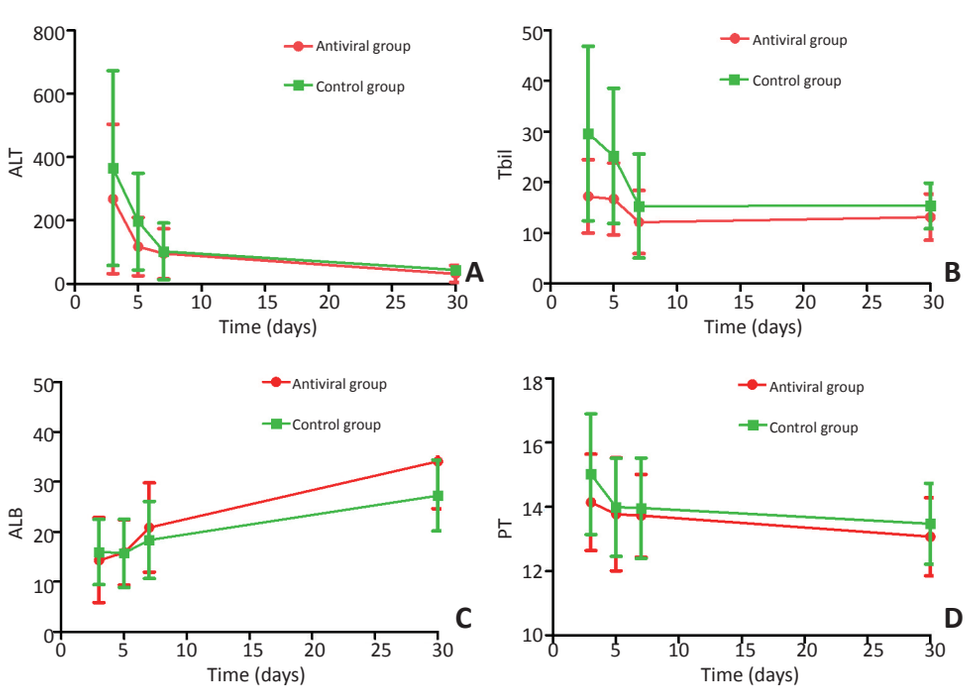
Clinical variable	Antiviral group (n=66)	Control group (n=108)	P
Gender (M/F)	58/8	92/16	0.617
Age (years)	49.97±9.71	49.67±12.22	0.904
BCLC-stage (A/B/C)	42/12/12	60/20/28	0.466

表1 患者一般临床特征 （续表1）

Table 1 Baseline characteristics of all included patients

Clinical variable	Antiviral group (*n*=66)	Control group (*n*=108)	*P*
Tumor numbers[&]			
<3	56	98	0.237
⩾3	10	10	
Tumor size (cm)			
>5	34	62	0.448
⩽5	32	46	
Preoperative tumor rupture (yes/no)	4/62	6/102	1.000*
Blood loss (mL)	348.42±303.73	359.26±219.74	0.848
Blood transfusion (yes/no)	2/64	8/100	0.322*
Operative time (min)	202.58±69.41	195.50±53.65	0.595
Tumor capsule (complete vs. absent+incomplete)	44/22	64/44	0.329
Anatomical hepatectomy (yes/no)	12/54	34/74	0.054
Inflow blood occlusion time (min)	28.03±25.40	24.98±38.88	0.690
Liver cirrhosis (present/absent)	54/12	87/21	0.837
AFP ⩾400 (ng/mL)**	32	50	0.779
PT (s)**	12.82±1.29	12.77±1.41	0.857
Total bilirubin (μmol/L)**	10.50±3.85	20.17±53.37	0.303
Albumin (g/L)**	40.24±5.19	42.57±4.61	0.032
ALT (IU/L)[&]	31.97±25.08	34.39±19.61	0.617
Ascites**			
Present	2	2	0.635
Absent	64	106	
Types of hepatectomy			
Major hepatectomy >3 liver segments	4	18	0.041
Minor hepatectomy ⩽3 liver segments	62	90	
Hepatitis B virus Pre-S1 antigen**			
Positive	46	60	0.064
Negative	20	48	

*. Fisher's exact tests (2-tailed); **. Preoperative indicators



►A. The postoperative liver function change of ALT for patients in antiviral group and control group; B. The postoperative liver function change of Tbil for patients in antiviral group and control group; C. The postoperative liver function change of ALB for patients in antiviral group and control group; D. The postoperative liver function change of PT for patients in antiviral group and control group

图1 抗病毒组与对照组术后肝功能指标比较

Figure 1 Comparison of liver function between patients in the antiviral group and control group

表2 围手术期HBV再激活单因素分析

Table 2 Univariate analysis of factors related to HBV reactivation during the perioperative period

Clinical variable	Reactivation group (*n*=32)	Non-reactivation group (*n*=142)	*P*
Gender (M/F)	28/4	122/20	1.000*
Age (years)	50.25±11.01	49.68±11.41	0.855
BCLC-stage (A/B/C)	2016/10/6	86/22/34	0.115
Tumorous numbers**			
<3	28	126	0.766*
≥3	4	16	
Tumor size (cm)			
>5	16	80	0.515
≤5	16	62	
Preoperative tumor rupture (yes/no)	2/30	8/134	1.000*
Blood loss (mL)	323.13±238.38	362.37±257.49	0.578
Blood transfusion (yes/no)	3/29	7/135	0.394*
Operative time(min)	194.38±53.26	199.04±61.52	0.780
Tumor capsule (complete vs. absent+incomplete)	20/12	88/54	0.956
Anatomical hepatectomy (yes/no)	8/24	38/104	0.838
Inflow blood occlusion time (min)	21.00±14.72	25.04±23.61	0.514
Liver cirrhosis（present/absent）	30/2	111/31	0.042
AFP (ng/mL)（≥400）**	12	70	0.227
PT (s)**	12.95±1.95	12.75±1.20	0.599
Total bilirubin (μmol/L)**	13.98±6.43	17.08±46.70	0.792
Albumin (g/L)**	44.68±2.12	41.01±5.15	0.007
ALT (IU/L)**	34.38±14.35	33.27±23.16	0.855
Ascites**			
Present	1	3	0.560*
Absent	31	139	
Types of hepatectomy			
Major hepatectomy >3 liver segments	24	128	0.020
Minor hepatectomy ≤3 liver segments	8	14	
Hepatitis B virus Pre-S1 antigen**			
Positive	20	86	0.839
Negative	12	56	
Antiviral therapy（yes/no）	2/30	64/78	<0.001

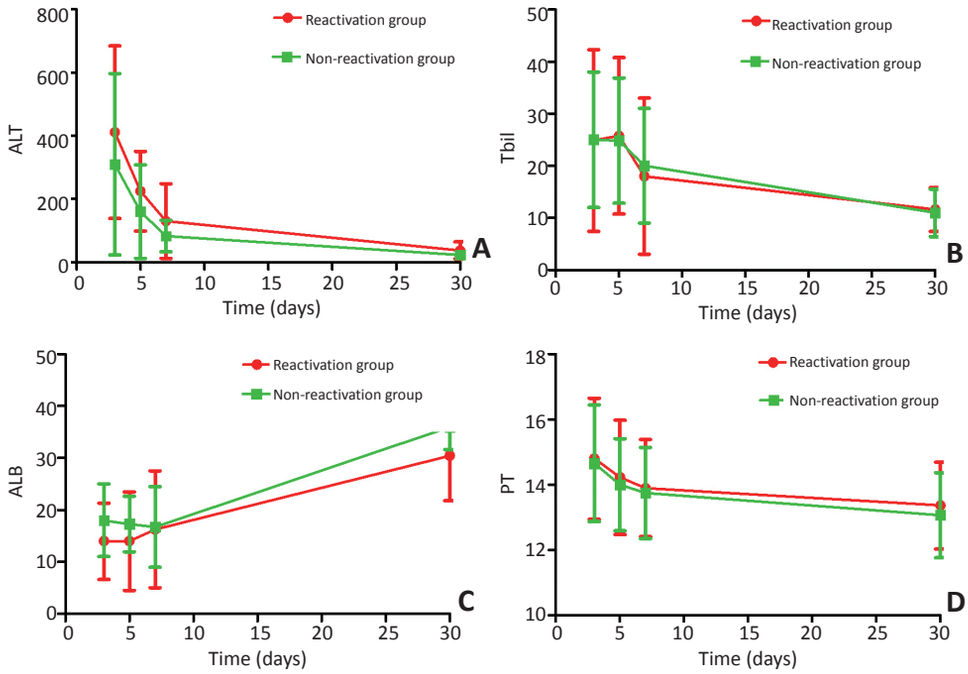
*. Fisher's exact tests (2-tailed); **. Preoperative indicators.

表3 围手术期HBV再激活logistic回归多因素分析

Table 3 Multivariate analysis using logistic regression analyses of factors related to HBV reactivation during the perioperative period

Variable	HR	95% CI	*P*
Liver cirrhoisis (present)	5.804	0.888-37.945	0.066
ALB ≤35 g/L*	0.452	0.045-4.569	0.501
Minor hepatectomy ≤3 liver segments	4.695	1.257-17.537	0.021
Without antiviral therapy	8.164	1.831-36.397	0.006

HR: hazard ratio; *. Preoperative indicators



▶A. The postoperative liver function change of ALT for patients in reactivation group and non-reactivation group; B. The postoperative liver function change of Tbil for patients in reactivation group and non-reactivation group; C. The postoperative liver function change of ALB for patients in reactivation group and non-reactivation group; D. The postoperative liver function change of PT for patients in reactivation group and non-reactivation group

图2 激活组与未激活组术后肝功能指标比较

Figure 2 Comparison of liver function among patients in reactivation group and non-reactivation group

3 讨论

核苷类似物是治疗慢性乙型病毒性肝炎最主要的抗病毒药物，然而却很难杀灭所有HBV，主要原因是肝细胞内存在共价闭合环状DNA（covalently closed circular DNA，cccDNA）。cccDNA作为微型染色体以组蛋白及非组蛋白的形式存在于感染HBV的肝细胞核内，只有彻底清除了细胞核内的cccDNA，才能彻底消除HBV。然而，目前没有能够彻底清除及抑制cccDNA的药物。核苷类似物可显著抑制术后HBV复制及再激活，由于恩替卡韦及替诺福韦的强效抑制病毒能力及低耐药性，国内外指南共识[4,6-7]建议作为抗HBV的一线治疗用药。研究表明，肝切除术、放疗、射频消融、肝动脉化疗栓塞、化疗等抗肿瘤治疗可导致基因扩增[5]最终导致HBV复制及再激活。

术前抗病毒治疗能有效防治HBV病毒再激活，减少肝功能损伤并降低术后复发风险，改善患者愈后[3,12]。2013年中华医学会肝病学分会肝癌学组制定的专家建议[8]中明确指出若术前HBV-DNA阳性应给予抗病毒治疗，对于HCC合并HBV-DNA阴性者，术前抗病毒治疗能否减少HBV再激活，目前缺乏高等级证据。建议[8]中还指出HBV-DNA阴性HCC患者接受经导管动脉化疗栓塞、放射治疗或全身化疗时，应密切监测HBV-DNA，若HBV-DNA为阳性，应给予抗病毒治疗。《慢性乙型肝炎防治指南（2015年版）》[13]中指出：在接受化疗、免疫抑制剂治疗的非活动性HBsAg携带者，治疗前应抗病毒治疗。然而，上述的专家建议和指南均未明确HCC合并HBV-DNA阴性者术前是否需抗病毒治疗。

Kubo等[14]研究报道了HCC患者肝切术后HBV再激活率为28%及34%诱发急性肝炎。一项前瞻性随机对照试验[15]表明对于HBV-DNA≥1.0×10^4 copies/mL的HCC患者肝切术后未抗病毒治疗HBV再激活率显著高于抗病毒者（31.8% *vs.* 2.5%，P<0.001）。有研究报道[2]对于术前HBV-DNA<2 000 IU/mL者，手术打击可导致19.1%的HBV再激活，HBV-DNA<2000 IU/mL及HBV再激活是HCC患者无瘤生存及总体生存时间的独立风险因素。这些研究表明肝切术术前宜常规使用抗病毒治疗。然而，对于HBV-DNA阴性HCC者尚无术前给予抗病毒治疗的研究。本研究纳入174例HBV-DNA阴性的HCC患者，研究结果显示，术前未抗病毒治疗导致HBV再激活率明显高于术前抗病毒者（27.8% *vs.* 3.0%，P<0.001）。

本研究发现小部分肝切术（≤3肝段）及术前未抗病毒治疗是术后HBV再激活的风险因素。术前未抗病毒治疗增加术后HBV再激活风险（HR=8.164，95% CI：1.831～36.397，P=0.006）。小部分肝切术较大部分肝切术（>3肝段）更易引起HBV再激活（HR=4.695，95% CI：1.257～17.537，P=0.021）。尽管关于小部分肝切术导致再激活原因尚不明确，然而理论上，大部分肝切术会将大量的HBV从肝细胞内移除，剩余HBV基数及肝体积偏小，短时间之内肝细胞再生能力下降，受HBV感染细胞随之减少，因此血清中较难检测出HBV。然而，小部分肝切术引起肝体积减少不明显，体内HBV基数较大且肝细胞再生能力较强，因此，HBV侵入再生肝细胞能力较强，从而围手术期内体内较易检测出HBV。本研究中心前期研究[16]所显示肿瘤直径5～10 cm的HCC患者行肝切术

是HBV再激活的独立风险因素。

目前公认术后HBV再激活可加剧肝功能损害。本研究表明对于术前是否抗病毒治疗以及术后HBV是否激活在肝切除术后1周对肝功能变化无明显影响。然而，比较术后30天肝功能发现，抗病毒组及未激活组相对于未抗病毒组及激活组在ALT及ALB方面差异具有统计学意义，前者指标较好。这种现象可能因术后第1周内肝功能指标主要受到手术等临床因素的影响，而HBV再激活导致的肝损害是一个慢性连续的过程，因此，术后1周肝功能指标未见明显的差异，而术后30天出现ALT及ALB的差异。

有研究[17]报道HCC行肝切除术后5年内复发高达75%，肿瘤一旦复发，需继续接受再次手术、肝动脉化疗栓塞、射频消融、放疗等多模式综合治疗，而这些治疗手段[3, 18-19]可导致HBV再激活及肝功能损害。因此，围手术期应密切监测HBV-DNA水平，一旦HBV再激活需积极给予抗病毒治疗。本研究尚需更大样本、设计更严谨的临床试验证实。

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