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肝癌乙型肝炎病毒感染患者术后恩替卡韦抗病毒治疗的临床疗效及安全性评价*

王棣祥[1] 王家兴[2] 吕文杰[1] 戢良银[1] 李 捷[2] 张 恒[2]

（1 攀钢集团总医院急诊科 四川 攀枝花 617023；2 攀钢集团总医院普外科 四川 攀枝花 617023）

摘要 目的：探讨肝癌乙型肝炎病毒(HBV)感染患者根治性切除术后采用恩替卡韦抗病毒治疗的临床疗效及安全性。**方法：**收集2015年1月-2017年8月在我院行根治性切除术的肝癌HBV感染患者279例为研究对象，以血清HBV-DNA载量10^5 copies/ml为界限，分为高病毒复制组128例，低病毒复制组151例，按照随机数字表法将高病毒复制组分为高-治疗组64例、高-对照组64例，将低病毒复制组分为低-治疗组76例、低-对照组75例。高-治疗组和低-治疗组术后给予恩替卡韦0.5 mg/d，高-对照组和低-对照组未行抗病毒治疗。比较手术前、术后7 d各组的血清HBV-DNA水平，血清白蛋白(ALB)、谷丙转氨酶(ALT)、前白蛋白(PA)，以及术后并发症的发生情况。**结果：**高-治疗组、高-对照组、低-治疗组、低-对照组术后血清ALB、PA均较治疗前降低，血清ALT均较治疗前升高，且高-治疗组或低-治疗组术后血清ALB、PA均高于高-对照组或低-对照组，血清ALT水平均低于高-对照组或低-对照组，差异均有统计学意义(P<0.05)；高-治疗组或低-治疗组术后血清HBV-DNA水平均低于治疗前，且均低于同期高-对照组或低-对照组，差异均有统计学意义(P<0.05)。高-治疗组与高-对照组、低-治疗组与低-对照组患者术后并发症发生率均无统计学差异(P>0.05)。**结论：**恩替卡韦能显著改善肝癌HBV感染患者术后的血清HBV-DNA载量水平和肝功能，安全性高，值得临床推广。

关键词：肝癌；乙型肝炎病毒感染；根治性切除术；恩替卡韦；抗病毒；疗效；安全性

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Evaluation of Clinical Efficacy and Safety of Entecavir Antiviral Therapy in Postoperative Liver Carcinoma Patients with Hepatitis B Virus Infection*

WANG Di-xiang[1], WANG Jia-xing[2], LV Wen-jie[1], JI Liang-yin[1], LI Jie[2], ZHANG Heng[2]

(1 Department of Emergency, General Hospital of Pangang Group, Panzhihua, Sichuan, 617023, China;

2 Department of General Surgery, General Hospital of Pangang Group, Panzhihua, Sichuan, 617023, China)

ABSTRACT Objective: To explore the clinical efficacy and safety of entecavir antiviral therapy in the treatment of liver carcinoma patients with hepatitis B virus (HBV)infection after radical resection. **Methods:** A total of 279 liver carcinoma patients with HBV infection, who underwent radical resection surgery in General Hospital of Pangang Group from January 2015 to August 2017, were selected as subjects and were divided into high viral replication group(n=128) and low viral replication group(n=151) according to the demarcation line of 10^5 copies/mL of serum HBV-DNA loading. The high virus replicating group was further divided into high treatment group(n=64) and high control group(n=64); the low virus replication group was further divided into low treatment group(n=76) and low control group (n=75) according to the random number table methods. The high treatment group and low treatment group were treated with entecavir 0.5 mg/d after surgery, but high control group and low control group were not treated with entecavir. The serum HBV-DNA level, serum albumin (ALB), alanine aminotransferase (ALT), prealbumin (PA) levels before surgery and 7 d after surgery were compared; the incidence rate of complications after surgery in each group were also compared. **Results:** The serum ALB, PA levels after surgery were lower than before surgery, and serum ALT was higher than before surgery in high treatment group, high control group, low treatment group, and low control group. The serum ALB, PA levels after surgery in high treatment group or low-treatment group were higher than high control group or low control group, and serum ALT level after surgery were lower than high control group or low control group, the differences were statistically significant (P<0.05). The serum HBV-DNA level after surgery in high treatment group or low treatment group were lower than before surgery, and lower than high control group or low control group in the same period, the differences were statistically significant(P<0.05). There was no significant difference in postoperative incidence rate of complications among high treatment group, high control group, low treatment group and low control group (P>0.05). **Conclusion:** Entecavir can significantly improve the serum HBV-DNA level and liver function of postoperative liver carcinoma patients with HBV infection, with highly safety, which is worthy of clinical promotion.

Key words: Liver carcinoma; HBV infection; Radical resection; Entecavir; Antiviral; Curative effect; Safety

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作者简介：王棣祥(1963-)，男，大专，主治医师，从事肝胆、胃肠外科、腹部损伤与急救方面的研究，E-mail：pwegoe@163.com

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前言

肝癌是临床常见的恶性肿瘤,其发病率和病死率分别占全球恶性肿瘤的第 5 位和第 3 位,我国肝癌发病人数占全世界的 55%,并有逐渐上升的趋势,严重威胁人们的健康和生活质量[1-3]。根治性切除术是目前临床治疗肝癌的常见手段,但是术后患者的复发率较高,5 年生存率较低,为 30%-50%[4-6]。肝癌患者多伴有乙型肝炎的病史,报道表明[7,8],乙型肝炎病毒(hepatitis B virus, HBV)的持续性感染是导致肝癌发生的重要危险因素。对合并 HBV 感染的肝癌患者进行抗病毒治疗,可有效降低患者体内的 HBV 复制,延缓肝癌的发生及发展[9,10]。核苷酸类似物是目前临床用于抗 HBV 治疗的常见药物,主要有恩替卡韦、拉米夫定等。本研究拟采用恩替卡韦对行根治性切除术的肝癌 HBV 感染患者进行抗病毒治疗,旨在探讨其临床疗效及安全性。现报道如下:

1 资料与方法

1.1 一般资料

收集 2015 年 1 月 -2017 年 8 月在我院行根治性切除术的的肝癌 HBV 患者 279 例为研究对象,纳入标准:(1)满足《原发性肝癌的临床诊断与分期标准》[11]的 HBV 感染的肝癌患者,患者均经临床病理及病原学确诊;(2)检测结果显示血清 HBV-DNA 载量≥ 10^3 copies/ml;(3)所有患者均接受根治性切除手术,且无手术禁忌症;(4)术前未进行任何形式的抗病毒治疗;(5)术前未接受其它可能影响本研究结果的治疗,如生物治疗、放化疗等;排除标准:(1)孕产妇,以及哺乳期的妇女;(2)心功能不全者;(3)肾功能障碍患者;(4)合并有其它病毒性感染。本研究获得医院伦理委员会通过,患者及家属签署知情同意书。

1.2 分组及治疗方法

以血清 HBV-DNA 载量 10^5 copies/ml 为界限,HBV-DNA ≥ 10^5 copies/ml 为高病毒复制组,共 128 例,HBV-DNA<10^5 copies/ml 为低病毒复制组,共 151 例。按照随机数字表法将高病毒复制组分为高 - 治疗组 64 例、高 - 对照组 64 例,将低病毒复制组分为低 - 治疗组 76 例、低 - 对照组 75 例,组间一般资料比较无统计学差异(P>0.05),均衡可比。见表 1。高 - 治疗组和低 - 治疗组患者根治性切除术手后即开始口服恩替卡韦分散片(正大天晴药业集团股份有限公司,国药准字:H20100019,规格:0.5 mg)0.5 mg/d,直到出院,高 - 对照组和低 - 对照组患者未接受抗病毒治疗,四组患者的术后保肝药物治疗以及对症支持治疗等一致。

表 1 各组患者临床资料分布及构成比(%)

Table 1 Constituent ratio of the clinical data in each group (%)

Items		High treatment group (n=64)		High control group(n=64)		Low treatment group (n=76)		Low control group(n=75)	
		n	Constituent ratio	n	Constituent ratio	n	Constituent ratio	n	Constituent ratio
Gender	Male	35	54.69	38	59.38	46	60.53	41	54.67
	Female	29	45.31	26	40.63	30	39.47	34	45.33
Age (years)	<60	39	60.94	32	50.00	43	56.58	46	61.33
	≥ 60	25	39.06	32	50.00	33	43.42	29	38.67
Clinical stage	Stage I	21	32.81	25	39.06	22	28.95	16	21.33
	Stage II	37	57.81	30	46.88	39	51.32	51	70.67
	Stage III	6	9.38	9	14.06	15	19.74	8	8.00
TNM stage	Stage I	20	31.25	17	26.56	18	23.68	19	25.33
	Stage II	30	46.88	28	43.75	32	42.11	37	49.33
	Stage IIIA	11	17.19	10	15.63	18	23.68	12	16.00
	Stage IIIB	3	4.69	9	14.06	8	10.53	7	9.33

1.3 观察指标

分别于手术前及手术后的第 7 d 检测血清 HBV-DNA 水平,肝功能指标包括血清白蛋白(albumin, ALB)、谷丙转氨酶(alanine aminotransferase, ALT)、前白蛋白(pre albumin, PA),以及并发症的发生情况。具体检测方法:收集患者清晨空腹肘静脉血 5 mL,以 2000 r/min 的速度离心 10 min,将上清液置于 -80℃环境下保存。血清 HBV-DNA 载量采用罗氏 480 型实时荧光定量聚合酶链反应仪(罗氏公司提供)检测,试剂盒由上海科华生物工程股份有限公司提供,并严格参照试剂盒上的说明进行相关操作,血清 ALB、ALT、PA 水平采用 OLYMPUS AU5400 型全自动生化分析仪(奥林巴斯中国有限公司提供)检测,试剂由上海复星长征医学科学有限公司提供,严格按照试剂盒上的说明进行操作。

1.4 统计学方法

SPSS19.0 软件录入数据及统计分析,ALB、PA 水平等计量资料以($\bar{x}\pm s$)表示,实施 t 检验或重复测量方差分析,计数资料以率(%)表示,实施 χ^2 检验,检验标准设置为 α=0.05。

2 结果

2.1 高病毒复制组手术前后血清 HBV-DNA 水平及肝功能指标比较

高病毒复制组中,高 - 治疗组和高 - 对照组术后血清 ALB、PA 较术前降低,血清 ALT 较术前升高,差异均有统计学意义(P<0.05),高 - 治疗组术后血清 HBV-DNA 低于术前,差

异有统计学意义（P<0.05），高 - 对照组手术前后血清 HBV-DNA 差异无统计学意义（P>0.05）；高 - 治疗组术后的血清 HBV-DNA、ALT 水平低于高 - 对照组，血清 ALB、PA 水平高于高 - 对照组，差异均有统计学意义（P<0.05），见表 2。

表 2 高病毒复制组手术前后血清 HBV-DNA 及肝功能指标比较（$\bar{x}\pm s$）

Table 2 Comparison of serum HBV-DNA and liver function indexes in high viral replication group before and after surgery（$\bar{x}\pm s$）

Groups	n	Times	HBV-DNA(log copies/ml)	ALB(g/L)	ALT(U/L)	PA(mg/L)
High treatment group	64	Before surgery	6.37± 0.58	41.37± 4.52	50.22± 19.68	211.35± 55.32
		After surgery	4.28± 0.66$^{\triangle\#}$	39.26± 5.01$^{\triangle\#}$	89.95± 21.34$^{\triangle\#}$	185.72± 57.98$^{\triangle\#}$
High control group	64	Before surgery	6.19± 0.71	40.68± 5.16	51.03± 18.90	198.96± 64.87
		After surgery	6.08± 0.69	33.71± 4.98$^{\triangle}$	133.06± 20.87$^{\triangle}$	154.04± 60.25$^{\triangle}$

Note: Compared with before surgery, $^{\triangle}$ P<0.05; Compared with high control group, $^{\#}$P<0.05.

2.2 低病毒复制组手术前后血清 HBV-DNA 水平及肝功能指标比较

低病毒复制组中，低 - 治疗组和低 - 对照组治疗后血清 ALB、PA 较术前降低，血清 ALT 较术前升高，差异均有统计学意义（P<0.05），低 - 治疗组术后血清 HBV-DNA 低于术前，差异有统计学意义（P<0.05），低 - 对照组手术前后血清 HBV-DNA 差异无统计学意义（P>0.05）；低 - 治疗组术后的血清 HBV-DNA、ALT 水平低于低 - 对照组，ALB、PA 水平高于低 - 对照组，差异均有统计学意义（P<0.05），见表 3。

表 3 低病毒复制组手术前后血清 HBV-DNA 及肝功能指标比较（$\bar{x}\pm s$）

Table 3 Comparison of serum HBV-DNA and liver function indexes in low viral replication group before and after surgery（$\bar{x}\pm s$）

Groups	n	Times	HBV-DNA(log copies/ml)	ALB(g/L)	ALT(U/L)	PA(mg/L)
Low treatment group	76	Before surgery	2.97± 0.52	43.75± 3.89	38.83± 17.52	239.91± 72.01
		After surgery	0.83± 0.59$^{\triangle\#}$	40.28± 3.73$^{\triangle\#}$	75.57± 18.20$^{\triangle\#}$	221.06± 71.22$^{\triangle\#}$
Low control group	75	Before surgery	2.83± 0.61	44.21± 3.50	40.02± 18.11	243.43± 69.87
		After surgery	2.77± 0.55	35.64± 3.92$^{\triangle}$	107.95± 18.00$^{\triangle}$	202.38± 72.34$^{\triangle}$

Note: Compared with before surgery, $^{\triangle}$ P<0.05; Compared with low control group, $^{\#}$P<0.05.

2.3 高病毒复制组及低病毒复制组术后并发症发生率

高 - 治疗组与高 - 对照组术后并发症总发生率分别为 6.25%、12.50%，两组比较差异无统计学意义（P>0.05），低 - 治疗组与低 - 对照组术后并发症总发生率分别为 6.58%、12.00%，两组比较差异无统计学意义（P>0.05），见表 4。

表 4 高病毒复制组及低病毒复制组术后并发症发生率[n(%)]

Table 4 Incidence rate of complications in high viral replication group and low viral replication group after surgery[n(%)]

Groups	n	Haemorrhage of digestive tract	Incisional infection	Biliary fistula	Ascites	Total
High treatment group	64	1(1.56)	0(0.00)	1(1.56)	2(3.13)	4(6.25)$^{\triangle}$
High control group	64	1(1.56)	2(3.13)	2(3.13)	3(4.69)	8(12.50)
Low treatment group	76	2(2.63)	1(1.32)	0(0.00)	2(2.63)	5(6.58)$^{\#}$
Low control group	75	4(5.33)	2(2.67)	2(2.67)	1(1.33)	9(12.00)

Note: Compared with High control group, x^2=1.471,$^{\triangle}$ P=0.225; Compared with low control group, x^2=1.319, $^{\#}$P=0.251.

3 讨论

据报道显示，每年全球肝癌的新发病例数超过 70 万，在我国，肝癌的新发病例数约占到全球发病例数的 1/2 及以上，肝癌现已成为威胁我国人群健康的重大公共卫生问题，肝癌根治性切除手术是目前临床治疗肝癌的有效手段之一[12-14]。由于肝癌的早期临床症状和体征无特异性，因此很多患者在确诊时已近中晚期，致使根治性切除术后患者的复发率较高，1 年内的复发率可高达 76%，并且 5 年生存率极低[15,16]。HBV 感染导致肝癌发生机制可能有如下原因[17-19]：（1）HBV-DNA 整合到宿主细胞的基因组增加了细胞基因的不稳定性，致使细胞生长的控制机制得以减弱；（2）HBV 感染导致炎症反应反复持续性的发作，致使受到损伤的肝细胞在反复多次的坏死和再生中发生基因变异，进一步引起新生细胞成为恶性细胞；（3）HBV 感染促进外源性的致癌因子作用增强，使其与其它的致癌因素发生协同效应而导致肝癌发生；（4）HBV 在细胞周期的调控过程中阻断了由 P53 介导的细胞凋亡过程，而使细胞线粒体功能等多个环节的通路受到影响，最终引起肝癌。因此，抗病毒治疗逐渐成

为根治性切除术后肝癌 HBV 感染患者治疗的常见措施。核苷类似物是临床常见的抗病毒治疗药物，研究证实，它能有效减弱患者体内 HBV 的复制能力，缓解炎症反应，同时减少 HBV-DNA 在细胞核内的整合，并最终预防肝癌的发生[20-22]。恩替卡韦作为临床常用的核苷类似物，它能选择性地抑制 HBV 的复制，其抗病毒机制为：通过磷酸化反应转化为具有活性的三磷酸盐，从而对前基因组 mRNA 逆转录负链的合成、以及多聚酶启动进行抑制，同时抑制 HBV-DNA 正链的合成，最终达到抗病毒的效果[23-25]。本研究以恩替卡韦对根治性切除术后肝癌 HBV 感染患者进行抗病毒治疗，旨在探讨其对的 HBV-DNA 水平及肝功能的影响。

ALT 是反映肝功能损伤程度最为敏感的指标，PA 则是体现肝功能储备能力常用的指标，ALB 是由肝脏合成的人体血清总蛋白中的主要蛋白质成分，是反映慢性肝损伤的指标之一，ALB、PA 水平越低，ALT 水平越高，说明肝功能损害越严重[26,27]。本研究结果显示，高病毒复制组和低病毒复制组患者根治性切除术后的血清 ALB、PA 均较术前降低，血清 ALT 较术前升高，说明无论高、低病毒复制组均出现了不同程度的肝功能损害，但经恩替卡韦治疗的患者其血清 ALT 水平低于未治疗患者，血清 ALB、PA 水平高于未治疗患者，提示对肝癌 HBV 感染患者术后进行恩替卡韦抗病毒治疗，可以明显改善患者的肝功能。可能与 HBV-DNA 整合到宿舍细胞的基因组中，使细胞基因的不稳定性增加，从而影响细胞生长的调控，而恩替卡韦能有效抑制 HBV-DNA 的复制以及整合，从而改善术后患者肝功能有关。HBV-DNA 是反映病毒复制能力的重要指标。本研究结果显示，高病毒复制组和低病毒复制组术后经恩替卡韦治疗后，血清 HBV-DNA 水平均较治疗前降低，且明显低于对照组。提示恩替卡韦抗病毒治疗能明显控制肝癌 HBV 感染患者术后 HBV 的复制能力，与有关研究结果一致[28-30]。术后高病毒复制组和低病毒复制组患者均发生不同程度的并发症，如消化道出血、切口感染、胆瘘以及腹水等，提示应密切关注行根治性切除术后肝癌 HBV 感染患者可能发生的并发症，及早采取护理干预措施。同时结果显示，高 - 治疗组或低 - 治疗组术后并发症总发生率略低于高 - 对照组或低 - 对照组（6.25% vs 12.50%，6.58% vs 12.00%），但组间比较差异均无统计学意义（P>0.05）。提示恩替卡韦抗病毒治疗并不会增加术后并发症发生风险，具有一定的安全性。

综上所述，恩替卡韦对肝癌 HBV 感染患者根治性切除术后的抗感染效果明显，可显著降低血清 HBV-DNA 载量水平，改善患者的肝功能，且并发症少，具有重要的临床推广价值。

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