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苦参碱联合恩替卡韦抗乙型肝炎病毒感染的作用及其机制 *

陈 曦[1] 任 浩[2] 陈照林[1] 董 静[1] 刘 波[1△]

(1 中国人民解放军第 105 医院感染病科 安徽 合肥 230031;2 安徽医科大学第二附属医院感染病科 安徽 合肥 230031)

摘要 目的:探讨苦参碱联合恩替卡韦治疗乙型肝炎病毒(HBV)感染的疗效并初步探讨其作用机制。**方法:**选择 2014 年 9 月 -2016 年 8 月我院收治的 HBeAg 阳性乙肝患者 98 例,按治疗方法分为对照组和观察组,每组 49 例。对照组患者给予恩替卡韦治疗,观察组患者在对照组基础上应用苦参碱联合治疗。分别在治疗后 12、24、48 周观察和比较两组患者的 HBeAg 转阴率、ALT 复常率、HBV DNA 转阴率、血清球蛋白水平。**结果:**观察组在治疗后 24、48 周的 HBeAg 转阴率、ALT 复常率、HBV DNA 转阴率均显著高于对照组,差异均具有统计学意义(P<0.05)。观察组血清球蛋白水平明显高于对照组,差异有统计学意义(P<0.05)。两组间不良反应发生情况比较差异无统计学意义(P>0.05)。**结论:**苦参碱联合恩替卡韦对于 HBV 具有较好的协同治疗作用,且安全性较好,可能与苦参碱降低血清转氨酶水平,增强患者免疫功能有关。

关键词:乙型肝炎;苦参碱;恩替卡韦

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Effects of Matrine Combined with Entecavir on Hepatitis B Virus Infection and Its Mechanisms*

CHEN Xi[1], REN Hao[2], CHEN Zhao-lin[1], DONG Jing[1], LIU Bo[1△]

(1 Department of Infectious Disease, The NO.105 Hospital of Chinese People's Liberation Army, Hefei, Anhui, 230031, China;

2 Department of Infectious Disease, The Second Hospital of Anhui Medical Hospital, Hefei, Anhui, 230031, China)

ABSTRACT Objective: To explore the effect and mechanism of matrine combined with entecavir on HBV. **Methods:** From September 2014 to August 2016, 98 cases of HBeAg positive hepatitis B patients in our hospital were selected as the study subjects, and they were divided into the control group and the observation group by treatment methods, 49 cases in each group. Patients in the control group were treated with entecavir, and patients in the observation group were treated with matrine combined with entecavir. At 12, 24 and 48 weeks after treatment, the HBeAg conversion rate, ALT recovery rate, HBV DNA conversion rate and serum globular protein level were observed and compared between the two groups. **Results:** The conversion rate of HBeAg, ALT and HBV DNA in the observation group were higher than those in the control group at 24 and 48 weeks after treatment (P<0.05). The level of serum globulin in the observation group was higher than that in the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusions:** Matrine combined with entecavir had a good synergistic therapeutic effect on HBV with high safety, it may be related to the reduction of serum aminotransferase levels and enhancement of immune function of patients with matrine.

Key words: Hepatitis B virus; Matrine; Entecavir

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前言

乙型肝炎病毒(hepatitis B virus,HBV)简称乙肝病毒,属于嗜肝 DNA 病毒科(hepadnaviridae),是目前已知的感染人最小的 DNA 病毒之一,也是最难治愈的病毒之一[1,2]。HBV 是一个双链 DNA 病毒,其复制存在着逆转录过程,即病毒基因组可以被整合到机体中是的机体难以将该病毒彻底清除,使得 HBV 感染长期持续存在,目前临床中可控制但不能彻底清除[3,4]。患者感染后,HBV 在肝细胞内复制是患者病情反复的主要原因。

目前,临床上主要采用核苷酸类似物治疗乙肝,如恩替卡韦、拉米夫定、阿德福韦酯等[5,6]。如恩替卡韦通过抑制 HBV DNA 聚合酶的活性抑制 HBV DNA 的复制[7,8]。近年来,研究显示苦参碱具有利尿、抗病原体、抗乙型和丙型肝炎病毒、改善肝功能等作用[9,10],作用机制与核苷酸类药物恩替卡韦不同[11,12]。此外,体外试验结果显示苦参碱与拉米夫定联合作用能显著增强对 HBV 的治疗效果[13]。因此,苦参碱联合恩替卡韦治疗 HBV

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作者简介:陈曦(1983-),男,本科,主治医师,研究方向:肝炎、肝硬化、肝衰竭的诊治,E-mail:chenxi001002003@163.com

△ 通讯作者:刘波(1972-),男,硕士,主任医师,研究方向:感染病防治,E-mail:liubo_1972@medpap2017.cn

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感染的疗效并初步探讨其作用机制。

1 资料与方法

1.1 一般资料

选择 2014 年 9 月 -2016 年 8 月于我院接受治疗的乙型肝炎患者 98 例,已排除其他病毒性肝炎及其他肝损害,患者在入院前未接受抗病毒药物治疗或免疫治疗。所有患者临床诊断均符合乙型肝炎的诊断标准。按治疗方法将患者分为对照组和观察组,每组 49 例。对照组男 32 例,女 17 例;平均年龄(36.2± 7.98)岁,平均病程(4.89± 2.03)年;HBV DNA(6.17± 1.21)log U/mL;丙氨酸氨基转移酶(ALT)为(55.24± 21.47)U/L。观察组男 34 例,女 15 例,平均年龄(37.5± 6.84)岁,平均病程(5.11± 2.37)年;HBV DNA(5.92± 1.54)log U/mL;丙氨酸氨基转移酶(ALT)为(51.73± 18.92)U/L。两组患者在年龄、性别、病程等一般资料比较差异均无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组患者每天 1 次给予恩替卡韦片(中美上海施贵宝制药有限公司,国药准字:H20052247) 0.5 mg,治疗 48 周。观察患者在对照组患者用药基础上同时给予静脉注射苦参碱注射液,每天 150 mg。(辽宁玉皇药业有限公司,国药准字:H20083501),治疗 48 周,嘱患者在治疗期间忌食辛辣刺激食品,禁饮酒及含酒精的饮料。

1.3 观察指标

分别于治疗前、治疗后 12、24、48 周检测 ALT、HBeAg/ 抗 HBe(采用化学发光法检测),HBV DNA (采用荧光定量 PCR 检测)。观察并比较 12 周、24 周和 48 周时两组患者 ALT 复常率,HBeAg/ 抗 HBe 血清转换率、HBV DNA 转阴率和球蛋白水平。ALT 复常率 = 复常患者例数 / 观察患者总数× 100%;HBV DNA 转阴率 = 转阴患者例数 / 观察患者总数× 100%。观察两组患者不良反应发生情况。

1.4 统计学分析

采用 SPSS 20.0 统计学软件分析,计量资料用($\bar{x}$± s)表示,组间比较采用 t 检验;计数资料采用率或构成比表示,组间比较采用 x^2 检验。以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床生化指标的比较

治疗 12 周时,两组患者的 ALT 复常率、HBeAg/ 抗 HBe 血清转换率和 HBV DNA 转阴率比较差异均无统计学意义(P>0.05);治疗 24 周和 48 周时,观察组 ALT 复常率、HBeAg/ 抗 HBe 血清转换率和 HBV DNA 转阴率均高于对照组,差异均有统计学意义(P<0.05)。见表 1。

表 1 两组治疗后临床生化指标比较[n=49, n(%)]

Table 1 The comparison of clinical biochemical indexes after treatment between two groups[n=49, n(%)]

Groups	ALT recovery rate			HEeAg conversion rate			HBV DNA conversion rate		
	12 w	24 w	48 w	12 w	24 w	48 w	12 w	24 w	48 w
Control group	7(14.29)	26(53.06)	36(73.47)	2(4.08)	5(10.20)	6(12.24)	4(8.16)	29(59.18)	33(67.35)
Observation group	8(16.33)	36(73.47)	44(89.80)	3(6.12)	13(26.53)	15(30.61)	5(10.20)	37(75.51)	42(85.71)
P	0.779	0.036	0.037	0.646	0.037	0.027	0.727	0.031	0.032

2.2 两组治疗前后血清球蛋白水平的比较

两组患者治疗 12、24、48 周时的血清球蛋白水平均比治疗前升高,且在治疗 24、48 时,观察组血清免疫球蛋白水平均显著高于对照组,差异均有统计学意义(P<0.05)。见表 2。

表 2 两组治疗前后血清球蛋白水平的比较 (n=49, $\bar{x}$± s)

Table 2 Comparison of the serum globular protein level before and after treatment between two groups(n=49, $\bar{x}$± s)

Groups	Globular protein level(g/L)			
	Before treatment	12 w	24 w	48 w
Control group	17.6± 5.2	18.7± 4.5	20.7± 5.8	24.2± 4.4
Observation group	17.1± 4.9	18.2± 5.1	23.6± 6.2	27.6± 5.7
P	0.625	0.608	0.019	0.001

2.3 两组不良反应发生情况的比较

治疗结束后,观察组 2 例患者出现腹泻、1 例乏力,对照有 2 例患者出现头晕。两组患者不良反应发生比较差异无统计学意义(P>0.05)。

3 讨论

HBV 感染是全球范围内常见的慢性病毒感染,呈世界性流行,而我国 HBV 感染率较高[14,15],加之人口基数大,故我国 HBV 感染者数量庞大,是值得全社会共同关注的公共健康问题。HBV 具有顽强的抵抗力、明显的嗜肝性、轻度的泛嗜性、严格的种属特性、变异性等特征,临床治疗可以控制但是不能彻底清除[16,17]。目前,临床上主要采用以恩替卡韦为代表的核苷酸类药物进行治疗,其主要通过抑制 HBV DNA 聚合酶抑制 HBV 复制,疗效较好[18,19]。然而,单一的恩替卡韦治疗却无法彻底根除 HBV,长期服用还有可能导致 HBV 基因变异,出现耐药性[20,21]。既往研究显示苦参碱具有抑制 HBV 的作用[22,23]。因此,本研究以苦参碱联合恩替卡韦用于治疗 HBV,以观察其联合作用的抗 HBV 疗效。

苦参具有清热解毒、养肝胆气、明目、祛风燥湿等功效，苦参碱是从苦参中提取的一种活性物质[24,25]。有研究显示苦参碱能直接抑制 HBV 基因表达来抑制乙肝病毒，从而改善 HBV 患者生化指标[26,27]。动物实验研究表明苦参碱能明显降低小鼠的血清转氨酶水平[28]，起到保肝护肝的作用。本研究结果显示在治疗 12 周时，组间 ALT 复常率、HBeAg/ 抗 HBe 血清转换率和 HBV DNA 转阴率差异不显著。在治疗 24 和 48 周时，观察组 ALT 复常率、HBeAg/ 抗 HBe 血清转换率和 HBV DNA 转阴率均高于对照组，表明苦参碱联合恩替卡韦有助于降低 HBV 患者血清转氨酶水平，且对于 HBV DNA 复制的抑制作用优于单独采用恩替卡韦治疗。此外，苦参碱能提升 HBV 患者的免疫功能，通过促进 B 细胞产生大量抗乙肝病毒抗体[29]，从而抑制 HBsAg 的分泌，用药期间观察组患者的球蛋白水平均显著高于对照组即可证明这点。

综上，苦参碱联合恩替卡韦对于 HBV 具有较好的协同治疗作用，且安全性较好，可能与苦参碱降低血清转氨酶水平，增强患者免疫功能有关。

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为革兰阳性菌和真菌。其中,革兰氏阴性菌主要为肺炎克雷伯杆菌(13/42),粘质沙门氏菌(7/42)。革兰氏阳性菌以凝固酶阴性葡萄球菌(7/19)为主[18],考虑与长时间肠外营养、接受侵入性治疗的机会多,抗生素的广泛使用有关[19]。本研究结果显示革兰阴性菌对大部分临床常用抗生素及三代头孢耐药,亚胺培南对其100%敏感;革兰阳性菌对β-内酰胺类、大环内酯类、氨基糖甙类耐药,对万古霉素、利奈唑烷敏感。因此,在早产极低/超低出生体重儿的诊治过程中,可根据病原菌构成及耐药性监测与研究,合理选用抗生素。虽血培养阳性率低,但目前仍无其他方法可替代,故使用抗生素前应尽早完善微生素培养和药敏实验[20],严格掌握抗生素使用指征,根据药敏结果和临床疗效选用药物,从而减少耐药菌株的发生。

综上所述,早产儿VLBWI/ELBWI败血症发生率、病死率较高,早期临床表现不典型,易漏诊误诊,延误治疗。临床治疗中,应注意动态监测血常规、CRP的变化,尽早完善细菌培养及药敏试验,有效合理使用抗生素,有助于早期诊断和改善预后。

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