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扶正化瘀胶囊联合微生态制剂和恩替卡韦治疗乙型肝炎病毒感染失代偿期肝硬化的临床研究*

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摘要 目的:探讨扶正化瘀胶囊联合微生态制剂和恩替卡韦治疗乙型肝炎病毒(HBV)感染失代偿期肝硬化的临床效果。**方法:**选取2015年6月~2019年6月期间我院收治的HBV感染失代偿期肝硬化患者73例,根据随机数字表法分为对照组(n=36)和研究组(n=37),对照组患者予以微生态制剂和恩替卡韦治疗,研究组则在对照组的基础上联合扶正化瘀胶囊治疗,比较两组患者疗效、T淋巴细胞亚群、肝功能[天冬氨酸氨基转移酶(AST)、总胆红素(TBIL)]以及肝纤维化指标[透明质酸(HA)、层黏连蛋白(LN)],记录两组乙肝表面e抗原(HBeAg)、乙肝病毒基因(HBV-DNA)转阴情况,记录两组不良反应发生情况。**结果:**研究组治疗6个月后的临床总有效率为91.89%(34/37),高于对照组的72.22%(26/36)($P<0.05$)。两组治疗6个月后AST、TBIL、HA、LN、CD8⁺均下降,且研究组低于对照组($P<0.05$)。两组治疗6个月后CD4⁺、CD4⁺/CD8⁺升高,且研究组高于对照组($P<0.05$)。两组治疗6个月后HBeAg、HBV-DNA转阴率比较无统计学差异($P>0.05$)。两组不良反应发生率对比未见统计学差异($P>0.05$)。**结论:**扶正化瘀胶囊联合微生态制剂和恩替卡韦治疗HBV感染失代偿期肝硬化疗效显著,虽在HBeAg、HBV-DNA转阴率方面未见明显改善,但可有效改善肝功能,减轻肝纤维化,提高机体免疫功能,且不增加不良反应发生率,安全性较好。

关键词:扶正化瘀胶囊;微生态制剂;恩替卡韦;乙型肝炎病毒;失代偿期肝硬化

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Clinical Study of Fuzheng Huayu Capsule Combined with Microecological Preparation and Entecavir in the Treatment of Decompensated Cirrhosis Due to Hepatitis B Virus Infection*

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ABSTRACT Objective: To investigate the clinical effect of Fuzheng Huayu capsule combined with microecological preparation and entecavir in the treatment of decompensated cirrhosis of hepatitis B virus (HBV) infection. **Methods:** 73 patients with decompensated cirrhosis of HBV infection who were admitted to our hospital from June 2015 to June 2019 were selected, they were divided into control group (n=36) and study group (n=37) according to the method of random number table. The control group was treated with microecological preparation and entecavir. The study group was treated with Fuzheng Huayu Capsule on the basis of the control group. The curative effect, T-lymphocyte subsea, liver function [aspartate aminotransferase (AST), total bilirubin (TBIL)] and liver fibrosis index [hyaluronic acid (HA), laminin (LN)] of the two groups were compared, the negative changes of hepatitis B surface e antigen (HBeAg) and hepatitis B virus gene (HBV-DNA) in the two groups were recorded, and the adverse reactions in the two groups were recorded. **Results:** The total clinical effective rate of the study group was 91.89% (34/37), which was higher than 72.22% (26/36) of the control group ($P<0.05$). AST, TBIL, HA, LN, CD8⁺ decreased in the two groups 6 months after treatment, and the level in the study group were lower than those in the control group ($P<0.05$). CD4⁺, CD4⁺/CD8⁺ increased in the two groups 6 months after treatment, and the study group were higher than those in the control group ($P<0.05$). There was no significant difference in the negative rate of HBeAg and HBV-DNA between the two groups ($P>0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Fuzheng Huayu capsule combined with microecological preparation and entecavir is effective in the treatment of decompensated cirrhosis of HBV infection. Although there is no significant improvement in HBeAg and HBV-DNA negative rate, it can effectively improve the liver function, reduce liver fibrosis, improve the immune function of the body, and do not

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increase the incidence of adverse reactions.

Key words: Fuzheng Huayu capsule; Microecological preparation; Entecavir; Hepatitis B virus; Decompensated cirrhosis

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前言

在我国,病毒性肝炎是导致肝硬化的最主要病因,而乙型肝炎病毒(Hepatitis B virus, HBV)的持续复制是肝硬化病情进展的根本原因^[1]。HBV 感染失代偿期肝硬化患者肝细胞受损严重,极易反复发作,若未及时进行干预,极有可能引发肝功能衰竭、肝肾综合征,预后较差^[2-4]。现临床有关 HBV 感染失代偿期肝硬化患者的治疗尚无特异性方案,多以抑制病毒复制,减轻肝纤维化,阻止疾病进展为主^[5,6]。微生态制剂联合恩替卡韦治疗是临床治疗该病的主要方案,其中恩替卡韦是临床上最常用的核苷类抗病毒药物,可有效抑制 HBV 复制^[7,8]。双歧杆菌三联活菌胶囊可通过改善患者肠道菌群分布而改善患者症状^[9]。然而仍有不少患者经此方案治疗后效果欠佳。扶正化瘀胶囊具有活血祛瘀、益精养肝的作用,可有效逆转肝纤维化,进而改善肝硬化临床症状^[10]。本研究通过探讨扶正化瘀胶囊联合微生态制剂和恩替卡韦治疗 HBV 感染失代偿期肝硬化的效果,以期临床治疗该病提供参考。

1 资料与方法

1.1 一般资料

选取 2015 年 6 月~2019 年 6 月期间我院收治的 HBV 感染失代偿期肝硬化患者 73 例。纳入标准:(1)失代偿期肝硬化的诊断标准参考《实用内科学》^[11];(2)乙肝表面 e 抗原(Hepatitis Be antigen, HBeAg)为阳性持续 6 个月以上,乙肝病毒基因(Hepatitis B virus-deoxyribonucleic acid, HBV-DNA) > 1000 copies/mL;(3)患者及其家属知情本研究且签署同意书;(4)治疗前半年未应用其他抗病毒或免疫调节药物。排除标准:(1)对本次研究用药存在过敏或禁忌症者;(2)合并严重心肺肾等脏器疾病者;(3)合并其他类型病毒性肝炎者;(4)未按医嘱用药,中途退出治疗者。根据随机数字表法分为对照组(n=36,微生态制剂和恩替卡韦治疗)和研究组(n=37,扶正化瘀胶囊联合微生态制剂和恩替卡韦治疗),其中对照组男 21 例,女 15 例,年龄 39~70 岁,平均(52.38±5.16)岁;乙肝病史 1~6 年,平均(3.15±0.82)年;肝硬化病史 0.8~4 年,平均(2.64±0.74)年;体质指数 21.6~26.8 kg/m²,平均(23.18±1.57) kg/m²。研究组男 23 例,女 14 例,年龄 36~72 岁,平均(51.96±4.74)岁;乙肝病史 2~8 年,平均(3.26±0.97)年;肝硬化病史 0.9~5 年,平均(2.75±0.86)年;体质指数 21.2~26.7 kg/m²,平均(23.09±1.25) kg/m²。两组患者一般

资料对比未见统计学差异($P>0.05$),具有可比性。本次研究已通过我院伦理学委员会批准进行。

1.2 方法

患者均进行常规保肝、清淡富营养饮食、给予健康指导、常规隔离等对症治疗。对照组患者在此基础上给予恩替卡韦(注册证号:H20150421, Swords Laboratories, 包装规格:2.5 kg/包, 5 kg/包)治疗,口服,0.5 mg/次,1 次/d;双歧杆菌三联活菌胶囊(国药准字 S10950032, 上海上药信谊药厂有限公司,规格:0.21 g),口服,0.63 g/次,3 次/d。研究组则在对照组的基础上联合扶正化瘀胶囊(国药准字 Z20020074, 上海黄海制药有限责任公司,规格:每粒装 0.5g),口服,5 粒/次,3 次/d。两组患者均连续治疗 6 个月。

1.3 观察指标

(1)记录两组治疗 6 个月后的临床疗效。疗效判定依据如下^[12]:显效:临床症状改善,肝功能均恢复正常,HBV-DNA 检测结果阴性者;有效:临床症状有所改善,肝功能处于恢复中,HBV-DNA 检测结果部分呈阴性者;无效:临床症状、肝功能均未见改善,HBV-DNA 检测结果阳性者。总有效率=显效率+有效率。(2)于治疗前、治疗 6 个月后采集患者清晨空腹静脉血 8 mL,经 4200 r/min 离心 11 min,离心半径 16 cm,分离上清液,置于冰箱(-30℃)中待测。采用美国贝克曼 AU-680 全自动生化分析仪检测肝功能指标:天冬氨酸氨基转移酶(Aspartate transaminase, AST)、总胆红素(Total bilirubin, TBIL)及肝纤维化指标:透明质酸(Hyaluronic Acid, HA)、层粘连蛋白(Laminin, LN)。采用 FACS-Calibur 流式细胞仪(美国 BD 公司生产)检测患者免疫功能指标:CD4⁺和 CD8⁺水平,并计算 CD4⁺/CD8⁺比值。分别采用酶联免疫吸附试验,荧光定量聚合酶链反应测定 HBeAg、HBV-DNA,试剂盒购自上海酶联生物科技有限公司,记录两组患者转阴率情况。(3)记录治疗过程中的不良反应。

1.4 统计学方法

使用 SPSS25.0 软件进行统计学分析,计量资料以($\bar{x} \pm s$)表示,比较实施 t 检验,计数资料以比或率表示,实施 χ^2 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 疗效比较

研究组治疗 6 个月后的临床总有效率为 91.89%(34/37),高于对照组的 72.22%(26/36)($P<0.05$);详见表 1。

表 1 疗效比较[例(%)]

Table 1 Comparison of clinical effects [n(%)]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group(n=36)	9(25.00)	17(47.22)	10(27.78)	26(72.22)
Study group(n=37)	14(37.84)	20(54.05)	3(8.11)	34(91.89)
χ^2				4.823
P				0.028

2.2 肝纤维化、肝功能指标比较

两组治疗前 AST、TBIL、HA、LN 比较差异均无统计学意

义($P>0.05$);两组治疗 6 个月后 AST、TBIL、HA、LN 均下降,且研究组低于对照组($P<0.05$);详见表 2。

表 2 两组患者肝功能、肝纤维化指标比较($\bar{x}\pm s$)

Table 2 Comparison of liver function and liver fibrosis indexes between the two groups($\bar{x}\pm s$)

Groups	AST(U/L)		TBIL($\mu\text{mol/L}$)		HA($\mu\text{g/L}$)		LN($\mu\text{g/L}$)	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group (n=36)	118.17 $\pm$ 6.53	59.46 $\pm$ 5.28*	53.26 $\pm$ 5.13	41.48 $\pm$ 3.22*	231.02 $\pm$ 19.38	102.77 $\pm$ 23.74*	151.59 $\pm$ 13.47	92.08 $\pm$ 16.89*
Study group (n=37)	117.64 $\pm$ 6.72	34.72 $\pm$ 4.52*	53.44 $\pm$ 6.25	29.67 $\pm$ 4.63*	227.73 $\pm$ 24.32	68.13 $\pm$ 17.63*	147.43 $\pm$ 16.57	64.37 $\pm$ 11.54*
t	0.342	21.526	0.134	12.620	0.638	7.091	1.177	8.204
P	0.734	0.000	0.894	0.000	0.525	0.000	0.243	0.000

Note: compared with before treatment, * $P<0.05$.

2.3 两组 T 淋巴细胞亚群比较

两组治疗前 CD4^+ 、 CD8^+ 、 $\text{CD4}^+/\text{CD8}^+$ 比较均无统计学差异

组($P<0.05$); CD4^+ 、 $\text{CD4}^+/\text{CD8}^+$ 均升高, 且研究组高于对照组($P<0.05$);详见表 3。

($P>0.05$);两组治疗 6 个月后 CD8^+ 均下降,且研究组低于对照

表 3 两组 T 淋巴细胞亚群比较($\bar{x}\pm s$)

Table 3 Comparison of T lymphocyte subsets between the two groups($\bar{x}\pm s$)

Groups	$\text{CD4}^+(\%)$		$\text{CD8}^+(\%)$		$\text{CD4}^+/\text{CD8}^+$	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group (n=36)	42.56 $\pm$ 5.04	49.38 $\pm$ 6.64*	34.58 $\pm$ 3.94	28.34 $\pm$ 3.18*	1.23 $\pm$ 0.27	1.74 $\pm$ 0.39*
Study group(n=37)	42.21 $\pm$ 4.61	57.51 $\pm$ 5.25*	34.19 $\pm$ 1.37	23.12 $\pm$ 3.28*	1.23 $\pm$ 0.35	2.49 $\pm$ 0.29*
t	0.310	5.812	0.568	6.901	0.000	9.341
P	0.758	0.000	0.572	0.000	1.000	0.000

Note: compared with before treatment, * $P<0.05$.

2.4 两组 HBeAg、HBV-DNA 转阴率比较

两组治疗 6 个月后 HBeAg、HBV-DNA 转阴率比较无统计

学差异($P>0.05$);详见表 4。

表 4 两组 HBeAg、HBV-DNA 转阴率比较 例(%)

Table 4 Comparison of the negative rates of HBeAg and HBV-DNA between the two groups n(%)

Groups	HBeAg negative conversion rate	HBV-DNA negative conversion rate
Control group(n=36)	24(66.67)	28(77.78)
Study group(n=37)	30(81.08)	34(91.89)
χ^2	1.969	2.840
P	0.161	0.092

2.5 不良反应发生率比较

治疗期间,对照组出现头痛 1 例、胃肠道不适 2 例、脱发 1 例,不良反应发生率为 11.11%(4/36);研究组出现头痛 1 例、脱发 1 例、胃肠道不适 3 例,不良反应发生率为 13.51%(5/37);两组不良反应发生率对比未见统计学差异($\chi^2=0.097$, $P=0.755$)。

3 讨论

肝硬化是一种不可逆转性疾病,进入晚期后,会导致肝功

能逐渐恶化,可并发上消化道出血、肝性脑病、腹水、感染等并发症,严重威胁患者生命安全^[13]。既往研究显示^[14],由 HBV 引起的肝细胞损伤是引发肝硬化和肝癌的主要原因。目前 HBV 感染已经成为全球共同面临的卫生问题,由于现今医学技术和药物效果有限,乙肝的患病率仍然较高,尤其是在经济相对不发达的地区。随着患者体内 HBV 的不断复制,患者免疫功能出现紊乱,引起肝功能损伤,而肝功能的损伤可导致进一步的肝内炎症,诱导肝纤维组织增生和肝硬化的形成^[15,16]。目前乙肝的

治疗通常选择口服核苷类抗病毒药物治疗^[17]。恩替卡韦由于服用方便,具有有效抑制病毒 DNA 合成、毒性相对低的特点,目前已经成为临床 HBV 感染失代偿期肝硬化患者的首选用药^[18,19]。既往有不少临床实践证实双歧杆菌三联活菌胶囊辅助治疗肝硬化具有较好的疗效^[20,21]。但包含双歧杆菌三联活菌胶囊在内的各种微生态制剂和恩替卡韦治疗仍无法有效调节患者的整体生理功能紊乱情况,部分患者的疗效仍不理想。扶正化癥胶囊的主要成分为丹参、五味子、冬虫夏草、桃仁、绞股蓝;马骁等学者的研究表明^[22],扶正化癥胶囊具有改善肝纤维化和肝功能,减轻炎症反应等作用。

本次研究结果显示,研究组治疗的疗效高于对照组,提示扶正化癥胶囊联合微生态制剂和恩替卡韦治疗 HBV 感染失代偿期肝硬化,可进一步提高治疗效果。恩替卡韦在 HBV 病毒复制的起始、反转录和合成等阶段均可发挥抑制作用;此外,恩替卡韦还可抑制肝脏内局部炎症反应,从而抑制肝脏的进一步纤维化^[23-25]。由于 HBV 感染失代偿期肝硬化患者肝功能受损,胆汁分泌障碍,进而导致肠道菌群失调,增加体内毒素含量。口服双歧杆菌三联活菌胶囊后可促进肠道有益菌繁殖,抑制并拮抗致病菌的繁殖,维持肠道菌群正常,同时还可修复肠黏膜上皮结构,保护其屏障功能^[26]。扶正化癥胶囊中的丹参、桃仁可活血化癥,五味子具有敛肺滋肾作用,绞股蓝能健脾益气、清热解毒,冬虫夏草疏肝理气、通络止痛,诸药合用,共奏活血祛瘀、益精养肝之效^[27,28]。上述药物从不同的作用机制出发,发挥协同作用,共同促进患者恢复。本次研究结果显示,两组患者肝功能、肝纤维化、免疫功能均有所改善,且研究组改善效果更佳。现代药理研究结果显示^[29,30],丹参、桃仁可促进肝细胞再生及抗肝纤维化,改善局部微循环;绞股蓝具有双向免疫调节、促进肝细胞的修复等作用;冬虫夏草具有清除自由基、提高抗氧化酶活性,提高机体免疫功能的作用。而本研究中两组治疗 6 个月后 HBeAg、HBV-DNA 转阴率比较无差异,本次研究联合用药未见显著提高 HBeAg、HBV-DNA 转阴率,可能是因为本次研究样本量偏小,有关联合用药在 HBeAg、HBV-DNA 转阴率方面的影响作用尚需通过扩大样本量进一步研究以证实。同时研究证实该联合治疗方案安全性较好,未见不良反应发生率的明显增加。

综上所述,扶正化癥胶囊联合微生态制剂和恩替卡韦治疗 HBV 感染失代偿期肝硬化,虽不能提高 HBeAg、HBV-DNA 转阴率,但疗效显著,可有效改善肝功能,减轻肝纤维化,提高机体免疫功能,且不增加不良反应发生率。

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