

·论 著·

丹参川芎嗪联合拉米夫定治疗慢性乙型肝炎肝纤维化的疗效

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摘要:目的 探讨丹参川芎嗪联合拉米夫定治疗慢性乙型肝炎(CHB)肝纤维化的效果。方法 选取60例慢性乙型肝炎患者随机分为治疗组和对照组,每组30例,治疗组予丹参川芎嗪联合拉米夫定,对照组单用拉米夫定,两组同时服用一般护肝药物(甘草甜素等),疗程为48周。结果 肝脏穿刺组织学检查结果显示:治疗组肝纤维化程度及肝纤维化指标改善明显,均优于对照组($P<0.01$);两组炎症活动度改善无明显差异。结论 丹参川芎嗪联合拉米夫定治疗慢性乙型肝炎肝纤维化效果明显优于单用拉米夫定,值得进一步研究。

关键词:乙型肝炎;慢性;肝纤维化;拉米夫定;丹参川芎嗪

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Effect of *Salvia miltiorrhiza* ligustrazine combined with lamivudine on liver fibrosis in chronic hepatitis B patients. LI San-qing NI Chuan-bin. (Department of Infectious Diseases of No. 425 Hospital of PLA, Sanya 572000, Hainan, P. R. China)

Abstract: Objective To investigate the *Salvia miltiorrhiza* Ligustrazine combined with lamivudine on hepatic fibrosis in chronic hepatitis B (CHB) patients. Methods Sixty patients with chronic hepatitis B were randomly divided into treatment group and control group each consisted of 30 cases. Patients in treatment group were treated with *Salvia miltiorrhiza* Ligustrazine combined with lamivudine, those in control group were treated with lamivudine, two groups taking general liver-protected drugs (glycyrrhizin etc.), treatment for 48 weeks. Results Liver biopsy showed: the liver fibrosis and liver fibrosis index in the treatment group improved significantly and superior to the control group ($P<0.01$); No significant differences were noticed in the two groups in the inflammation. Effect of combined use of lamivudine on liver fibrosis in chronic hepatitis B was superior to the single methods. Conclusion *Salvia Ligustrazine* combined with lamivudine is effective on liver fibrosis in chronic hepatitis B patients and worthy of further observation.

Key words: Hepatitis B; chronic; Liver fibrosis; Lamivudine; *Salvia Ligustrazine*

肝纤维化是继发于各种形式的慢性肝损伤之后肝组织修复过程中的代偿反应,是“慢性肝炎-肝纤维化-肝硬化”这一发展过程的枢纽环节^[1-2],三者之间无明显的界限,慢性乙型肝炎在不同阶段均存在不同程度的肝纤维化,抗肝纤维化就成了延缓或阻断慢性乙型肝炎发展成肝硬化的关键。现采用丹参川芎嗪联合拉米夫定治疗慢性乙型肝炎肝纤维化取得了较好的效果。

1 对象与方法

1.1 对象 选择2010~2012年在我科住院的CHB患者60例,年龄35~55岁,随机分为两组:治疗组30例(男16例,女14例),平均年龄37.6岁,病程3.57(6.80±2.51)年。对照组30例(男18例,女12例),平均年龄36.8岁,病程3.45(5.92±2.64)年。均排除标准:其它原因(其它病毒感染、酒精性、脂肪肝等)所致的慢性肝炎;既往接受过抗病毒治疗和免疫调节药物治疗;伴有其它严重的疾病,目前有肝硬化(肝功能失代偿);高胆红素血症;肝癌;妊娠;血液系统疾病等情况等患者。两组在性别、年龄、病程等均无统计学意义($P>0.05$)。诊断符合《慢性乙型肝炎防治方案》诊断标准

[3]。

1.2 方法 肝脏穿刺活体组织检查(肝活检)要求所有患者均在治疗前及治疗48周后做肝活检。肝活检前抽血检查血分析,凝血四项均在正常范围内,向患者说明肝活检的必要及可能存在的风险,并在诊疗操作知情同意书上签字;5例(治疗组2例,对照组3例)担心可能存在的风险,不同意做肝活检,2例因工作忙没有做第二次肝活检。均在超声定位后,按肝穿刺操作常规用16G穿刺针行肝脏穿刺,要求穿刺出的肝组织长度约2~3cm左右。取得的肝组织标本用10%甲醛溶液固定,送病理科,进行HE染色及网状纤维染色,病理医师诊断按《乙型肝炎临床与活体组织病理》标准^[4],炎症活动度分级为G0~G4,纤维化程度分期为S0~S4。治疗组30例患者用拉米夫定(葛兰素史克公司)10mg/d,口服,1次/d,同时服用丹参川芎嗪片(贵州拜特制药股份有限公司)口服4片/次,3次/d,对照组患者服用拉米夫定片100mg/d,1次/d;治疗过程中两组患者均予常规护肝药物(如甘草甜素等)对症治疗;疗程为48周。治疗过程中每3个月检测血清HBV-DNA定量,乙肝两对半,必要时检查血常规及

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肾功能等,观察用药后的不良反应。

1.3 观察指标 根据中华医学会肝纤维化组有关肝纤维化诊断及疗效评估共识标准^[4],分别于治疗前和治疗后用抽血检查肝纤维化指标(血清透明质酸(HA),Ⅲ型前胶原(PCⅢ)、Ⅳ型胶原(Ⅳ-C)、层粘连蛋白(LN)。试剂由北京泰格科信生物技术有限公司提供。

1.4 统计学处理 应用SPSS13.0统计学处理软件进行数据分析。数据计量资料 $\bar{x}\pm s$ 表示,两组间的比较用 t 检验及 χ^2 检验。 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组治疗前后肝组织病理变化 两组治疗前炎症及纤维化程度差异无统计学意义,治疗后炎症活动度无统计学意义,但肝纤维化程度改善情况治疗组明显优于对照组,差异有统计学意义,表1-2。

表1 两组治疗前后肝脏炎症活动度变化(例)

Table 1 Degree of inflammation before and after treatment (cases)

组别 Group		炎症活动度 Degree of inflammation			
		G1	G2	G3	G4
治疗组 Treatment	治疗前 Before	0	10	14	4
	治疗后 After	1	16	9	0
对照组 Control	治疗前 Before	0	7	18	2
	治疗后 After	0	14	11	2

注:两组治疗前后比较 $P>0.05$

表3 两组患者治疗前后肝纤维化指标比较

Table 3 before and after treatment in the two groups of patients with hepatic fibrosis index

组别 Group		例数 No.cases	HA(ng/ml)	PC Ⅲ (ng/ml)	Ⅳ-C(ng/m)	LN(ng/ml)
治疗组 Treatment	治疗前 Before	30	257.7±43.26	291.1±24.51	187.82±44.19	117.33±80.32
	治疗后 After		118.93±53.78	126.3±12.53	105.19±32.57	95.45±36.43
对照组 Control	治疗前 Before	30	160.5±107.34	224.8±22.59	299.62±58.48	259.79±83.03
	治疗后 After		138.79±69.42	174.1±61.57	231.69±41.37	206.12±50.14

注:与对照组比较 $P<0.01$;与治疗前比较 $P<0.01$

的微循环,促进肝细胞再生^[6];其主要作用机制是抑制TCF- β 和IL-6产生,减少胶原蛋白的合成,促进自由基清除,降解和吸收已沉积纤维成分,抑制炎症因子的释放,抑制肝星状细胞活化,有效抑制肝纤维化的进展^[7-8]。临床研究也证实丹参川芎嗪能够改善肝脏微循环,促进肝细胞修复与再生,调解体液免疫和细胞免疫,能抑制肝细胞脂质过氧化反应及肝内炎症反应,使血清Ⅲ型前胶原、透明质酸水平明显下降,肝炎症状得到明显改善,延缓病情进展^[9]。川芎嗪作用机制为通过抑制形状细胞的活化和增殖,抗脂质过氧化,减少胶原的合成,抑制肝细胞凋亡^[10-12],实现抗肝纤维化,改善肝功能的作用。

表2 治疗前后肝纤维化程度变化(例)

Table 2 Degree of liver fibrosis before and after treatment (cases)

组别 Group		肝纤维化程度 Degree of liver fibrosis			
		S1	S2	S3	S4
治疗组 Treatment	治疗前 Before	0	10	11	7
	治疗后 After	2	14	9	1
对照组 Control	治疗前 Before	0	14	8	5
	治疗后 After	1	9	13	4

注:两组治疗前比较 $P>0.05$,治疗后比较 $P<0.05$

2.2 治疗前后肝纤维化指标比较 联合治疗组患者治疗48周后HA、PCⅢ、Ⅳ-C、LN与治疗前比较均有不同程度的下降,两组间比较具有显著性差异($P<0.01$),表3。

3 讨论

由于HBV的复制和机体免疫清除作用持续存在,导致肝细胞炎症、坏死形成肝纤维化,肝纤维化进一步发展为肝硬化,肝纤维化是可逆^[5],而肝硬化不可逆转。因此延缓、阻断、甚至逆转肝纤维化,是阻止肝硬化的关键。

拉米夫定是最早应用于临床抗乙型肝炎病毒的核苷类似物,可以掺入乙肝病毒DNA合成过程中,但不能合成正常功能的核苷酸链,从而使HBV复制终止,主要抑制乙肝病毒DNA多聚酶和逆转录酶活性,从而达到减少病毒数量,减轻肝脏炎症。丹参能提高细胞超氧化物歧化酶的活性,清除自由基,改善肝脏

本组研究表明,对照肝活检结果发现,治疗组治疗结束后肝纤维化改善程度,血清肝纤维化指标(HA、PCⅢ、Ⅳ-C、LN)下降,均优于对照组,差异有统计学意义($P<0.05$),在慢性乙型肝炎的治疗中,抗病毒治疗是重点^[13],联合丹参川芎嗪活血化瘀治疗,能够发挥优势互补;有利于阻止或延缓肝纤维化的进展,控制或减轻肝内炎症活动,有一定的推广应用价值。

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