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阿魏酸钠联合双黄连注射液对病毒性心肌炎患者临床疗效及血清基质金属蛋白酶、锌铜水平的影响*

陈亚伟[1] 彭道地[2] 李绍冰[3] 黄 忠[1] 邸 杰[1] 张欣欣[1]

（1 保定市第一中心医院 心内科 河北 保定 071000；2 中南大学湘雅医院 心内科 湖南 长沙 410008；
3 河北省人民医院 心内科 河北 石家庄 050057）

摘要 目的：探究阿魏酸钠联合双黄连注射液对病毒性心肌炎患者临床疗效及血清基质金属蛋白酶、锌铜水平的影响。**方法：**选择在我院确诊为病毒性心肌炎的患者39例，随机分成实验组以及对照组。对照组18例给予阿魏酸钠治疗；实验组21例予阿魏酸钠联合双黄连注射液治疗。治疗14天后，评价和比较两组患者的临床疗效、心肌酶谱水平、血清基质金属蛋白酶水平及血清锌铜比值。**结果：**实验组总有效率为95.2%，显著高于对照组(72.2%)，差异具统计学意义(P<0.05)。与对照组比，实验组治疗后的血清、乳酸脱氢酶(LDH)水平、肌酸磷酸激酶同工酶(CK-MB)、天冬氨酸氨基转移酶(AST)、基质金属蛋白酶水平较低，血清铜锌比值较小，而左室射血分数(LVEF)水平较高，差异均具有统计学意义(P<0.05)。**结论：**阿魏酸钠联合双黄连注射液治疗病毒性心肌炎患者能够有效提高其临床疗效，可能与其显著降低血清基质金属蛋白酶及铜锌水平有关。

关键词：病毒性心肌炎；阿魏酸钠；双黄连注射液；基质金属蛋白酶；锌；铜

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Effect of Sodium Ferulic Acid Combined with Shuang Huang Lian Injection on the Clinical Efficacy and serum Matrix Metalloproteinases, Zinc and Copper Levels of Patients with Viral Myocarditis*

CHEN Ya-wei[1], PENG Dao-di[2], LI Shao-bing[3], HUANG Zhong[1], DI Jie[1], ZHANG Xin-xin[1]

(1 Department of Cardiology, Baoding First Central Hospital, Baoding, Hebei, 071000, China;
2 Department of Cardiology, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China;
3 Department of Cardiology Hebei People's Hospital, Shijiazhuang, Hebei, 050057, China)

ABSTRACT Objective: To investigate the effect of sodium ferulic acid combined with shuanghuanglian on the serum levels of matrix metalloproteinases, serum zinc and copper and clinical efficacy on the treatment of viral myocarditis. **Methods:** 39 patients with viral myocarditis from our hospital were selected and randomly divided into the control group and the experiment group. 18 cases in the control group were treated with sodium ferulic acid and 21 cases in the experiment group were treated with sodium ferulic acid combined with shuanghuanglian injection. Then the clinical efficacy, the serum levels of myocardial enzyme, matrix metalloproteinases and serum zinc copper ratio changes were observed and compared between two groups before and after the treatment. **Results:** The total effective rate of the experimental group was 72.2%, which was higher than 95.2% of the control group, and the difference was statistically significant (P<0.05); Compared with the control group, the serum levels of matrix metalloproteinases, copper and zinc ratio were lower the levels of lactate dehydrogenase (LDH), creatine kinase isoenzyme (CK-MB) and aspartate aminotransferase (AST) were lower, while the left ventricular ejection fraction (LVEF) was higher in the experiment group, and the differences were statistically significant (P<0.05). **Conclusions:** Sodium ferulate combined with shuanghuanglian injection has better clinical effects on the treatment of viral, which can effectively improve the symptoms, the heart function and clinical efficacy, and decrease the levels of matrix metalloproteinases and copper zinc ratio.

Key words: Viral myocarditis; Sodium ferulic acid; Shuanghuanglian injection; Matrix metalloproteinases; Zinc; Copper

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前言

病毒性心肌炎属炎症性心肌疾病，患者多因感染柯萨奇病毒而发病，感染病毒后既可以直接损伤患者心肌细胞，同时免疫细胞释放的自由基会加重对心肌细胞的损害程度，常为心肌非特异性间质性炎症[1,2]。在前驱症状如发热、流涕等症状出现

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作者简介：陈亚伟(1981-)，女，本科，主治医师，研究方向：冠心病，电话：13582291659

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后的 1 至 3 周,患者会发生心脏受累的表现。多数患者因心律失常症状而就诊,常表现为心悸、乏力及胸闷等。流行病学统计显示[3]男性病毒性心肌炎患者多于女性,其中约有 5%的患者会累及心脏而出现心律失常等症状。临床上治疗病毒性心肌炎的药物包括西药、中药及生物制剂等。阿魏酸钠广泛存在于植物界,是药物中的活性成分,不仅具有抗炎抗氧化的作用,还可以抑制血小板聚集,能够减轻对心肌细胞的损伤程度[4]。双黄连注射液由金银花、连翘等有效成分制成,具有清热解毒的功效,尤其适用于病毒感染的患者[5]。本实验通过观察阿魏酸钠联合双黄连注射液治疗病毒性心肌炎患者的临床疗效及其对患者血清基质金属蛋白酶、锌铜水平的影响,旨在探究阿魏酸钠联合双黄连注射液治疗病毒性心肌炎患者的临床疗效及可能机制。

1 资料与方法

1.1 病例选择

选择我院收治的病毒性心肌炎患者 39 例, 随机划分成实验组与对照组。对照组 18 例,包括 10 例男性,8 例女性,年龄 19~35 岁,平均为(23.1± 2.4)岁,病程为 8~19 天,平均患病(12.8± 1.5)天;实验组 21 例,包括 12 例男性及 9 例女性,年龄 20~34 岁,平均为(24.7± 2.5)岁,病程 7~21 天,平均(13.5± 1.5)天。两组性别及年龄等经比较差异不具备统计学意义(P>0.05)。本研究获得本院伦理委员会批准,告知患者并已签署知情同意书。依照 " 全国心肌炎心肌病研讨会纪要 " 中病毒性心肌炎的诊断标准纳入符合条件患者。排除扩张性心肌病;甲状腺功能亢进;风湿性心脏病;感染性心内膜炎;围生期心肌病;心脏瓣膜疾病;对药物过敏者;妊娠及哺乳期妇女。

1.2 治疗方法

嘱两组患者卧床休息,多食用低脂肪容易消化以及粗纤维的食物,做到饮食规律少食多餐;提高新鲜蔬菜水果摄入量;不食用油腻和刺激性的食物,如辛辣食物及咖啡等。对照组予阿魏酸钠注射液 (湖南恒生制药股份有限公司, 国药准字 H20055852)300 mg,溶于 250 mL 0.9%氯化钠注射液,每日一次,静脉滴注;实验组予阿魏酸钠注射液(湖南恒生制药股份有限公司,国药准字 H20055852)300 mg,抽吸后注入 250 mL 的 0.9%氯化钠注射液,每日一次,静脉滴注,双黄连注射液(吉林省辉南辉发制药股份有限公司, 国药准字 Z22022739)20 mL,溶于 0.9%氯化钠 250 mL 注射液,每日一次,静脉滴注。14 天为一个疗程。分别于治疗前后采集患者血清,嘱咐患者晨起空腹,在肘静脉处抽血 5 mL, 将抽得血样装进已经充有 EDTA 的抗凝采血管,按照 3000 r/min 转速离心血清 10 min,将上层液体吸出,放于 EP 管保存,将 EP 管放在 -20℃冰箱中备用。测定治疗前后两组血清锌铜水平及基质金属蛋白酶水平。比较两组患者的心肌酶谱变化。

1.3 检测方法

采用双抗体夹心酶联免疫吸附法(ELISA)测定各项指标。基质金属蛋白酶的检测选择由南京金益柏生物科技有限公司提供的试剂盒检测,血清锌铜水平选择上海江莱生物科技有限公司生产的试剂盒进行测定,以上操作均严格按照盒上操作说明及步骤进行检测。

1.4 疗效及不良反应评价

根据临床疗效痊愈、显效及无效三个等级来评价治疗效果。痊愈:患者心肌酶谱指标恢复正常,心悸乏力等症状消失;显效:患者心肌酶谱水平有所改善,但未到正常水平值,心悸乏力等症状发生次数少或程度减轻;无效:患者心悸乏力等症状仍存在,程度未减轻,心肌酶谱指标没有明显变化。总有效率 = (痊愈患者数 + 显效例数)/ 病历总数× 100%。密切观察所有研究对象,注意监测血压变化情况,当出现胸闷,血压下降等表现时,要警惕过敏性休克的发生,即使停药,注射肾上腺素及地塞米松进行治疗。

1.5 统计学分析

将数据输入统计学软件 SPSS 19.0 进行对比分析, 呈现正态分布的数据以 "$\bar{x}$± s" 来表示,采用 t 检验,两组计数资料数据以率(%)表示,采用卡方检验,当 P<0.05 时为差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

实验组总有效率为 95.2%,显著高于对照组(72.2%),差异存在统计学意义(P<0.05)。见表 1。

表 1 两组患者治疗后临床疗效的比较【例(%)】

Table 1 Comparison of the clinical curative effect between two groups after treatment[n(%)]

Groups	Cases	Cure	Excellent	Invalid	Total clinical curative effect rate
Control group	18	6(33.3)	7(38.9)	5(27.8)	13(72.2)
Experimental group	21	11(52.4)	9(42.9)	1(4.8)	20(95.2)*

Note: Compared with the control group, *P<0.05.

2.2 两组患者治疗前后心肌酶谱及 LVEF 水平对比

两组患者治疗后 LVEF 水平升高,CK-MB、LDH 及 AST 水平均下降;与对照组对比,实验组 LVEF 水平较高,CK-MB、AST 及 LDH 水平较低,差异存在统计学意义(P<0.05)。见表 2。

2.3 两组治疗前后血清基质金属蛋白酶及锌铜水平的比较

治疗后,两组患者基质金属蛋白酶水平及血清铜锌比值均较治疗前显著降低,与对照组对比,实验组患者血清铜锌比值较小,基质金属蛋白酶水平较低,差异均具有统计学意义(P<0.05)。见表 3。

3 讨论

病毒性心肌炎多因柯萨奇病毒而引起,造成心肌细胞弥漫性的心肌炎性病变,起初病毒能够直接攻击心肌细胞,在损伤部位生成毒素,诱发心肌纤维出现溶解甚至水肿坏死等[6]。随着

发展体内病毒会启动体内的免疫反应，免疫细胞释放大量氧自由基，造成心肌细胞进一步损伤，破坏线粒体功能，造成心肌代谢障碍的进一步加重[7]。病毒性心肌炎的表现具有个体差异，但大多数患者以心律失常为首发症状就医，主要表现为心悸、胸闷及头晕等，严重时可表现为心脏明显扩大出现心脏杂音等表现[8]。

表 2 两组患者治疗前后心肌酶谱及 LVEF 水平对比($\bar{x}\pm s$)

Table 2 Comparison of the myocardial enzyme spectrum and LVEF levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	CK-MB(U/L)		AST(U/L)		LDH(U/L)		LVEF(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	49.6± 5.2	41.2± 4.3*	57.4± 6.1	52.4± 5.6*	211.6± 21.7	194.3± 20.1*	50.9± 5.2	52.8± 5.7*
Experimental group	50.3± 5.3	22.2± 2.5*#	57.9± 6.2	41.2± 4.3*#	213.1± 22.7	169.8± 17.5*#	50.2± 5.3	67.2± 6.9*#

Note: Compared with before treatment,*P<0.05. Compared with the control group after treatment, #P<0.05.

表 3 两组患者治疗前后血清基质金属蛋白酶及锌铜水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum matrix metalloproteinases and zinc and copper levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	(μg/L) matrix metalloproteinases		(μmol/L) Zinc ion		(μmol/L) copper ion		Cu / Zn ratio	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	38.2± 3.9	36.8± 0.2*	11.3± 1.4	12.8± 1.6*	17.3± 1.8	17.6± 1.9	1.5± 0.2	1.3± 0.1*
Experimental group	39.1± 4.1	27.4± 2.9*#	11.5± 1.6	15.7± 1.7*#	17.1± 1.8	18.2± 1.9	1.4± 0.2	1.1± 0.1*#

Note: Compared with before treatment,*P<0.05. Compared with the control group after treatment, #P<0.05 .

阿魏酸钠主要是取自川芎及当归等中药的有效成分，具有抗凝及抑制血小板聚集等功能。当归性温味甘，具有活血止痛抑制血小板聚集的功能，并且能有效改善患者的心律失常症状[14,15]。川芎性温具有活血止痛功效，其中含有有效成分如酚类物质阿魏酸。阿魏酸钠能够有效清除体内的氧自由基水平，使内皮细胞损伤得到修复，促进心肌缺血部位血流恢复，有助于炎症改善[16]。双黄连注射液主要成分金银花、连翘等，具有清热解毒作用，在治疗病毒性呼吸道感染及肺炎等疾病时疗效显著[17]。双黄连注射液中的成分主要是大分子物质，过敏体质患者在使用双黄连注射液时易发生过敏性休克，因此在选用双黄连注射液前及注射中，应仔细询问过敏史，密切注意患者的血压心率变化[18]。本研究结果显示阿魏酸钠联合双黄连注射液治疗的患者总有效率为 95.2%，显著高于单用阿魏酸钠治疗，且患者 LVEF 水平较高，CK-MB、AST 及 LDH 水平较低，提示双黄连注射液可提高阿魏酸钠治疗病毒性心肌炎的临床疗效，有效减轻心肌损伤。此外，本实验使用阿魏酸钠联合双黄连注射液治疗病毒性心肌炎患者时，仅有 1 例使用双黄连注射液的患者出现血压降低及口唇发绀，立即停药后予肾上腺素及地塞米松治疗，症状得到有效缓解，提示其安全性较高。

基质金属蛋白酶属于一类酶的总称，依赖人体内钙离子及锌离子发挥作用而得名[9]。基质金属蛋白酶家族能够降解细胞外基质成分，破坏肿瘤细胞侵袭屏障，参与细胞外基质的重建过程 [10]。病毒性心肌炎患者的心肌细胞出现非特异性炎症改变，引起心功能障碍。人体内基质金属蛋白酶水平的变化说明心肌细胞外基质结构改变使胶原纤维水平降低，刺激胶原纤维生成，导致心室重塑及心功能不全的发生[11]。基质金属蛋白酶及 CK-MB 水平均可以反应病毒性心肌炎患者心肌细胞损伤的有效指标，能够判断心肌细胞损伤程度并对预后进行判断[19,20]。锌铜元素是人体内的必需元素，含量虽少，但作用广泛，人体内的多种酶类均为锌依赖性，能够调节生长发育及免疫等多个方面；锌元素对人体心肌细胞具有保护作用，当心肌出现病变发生坏死时，体内锌的含量会降低[12]。体内的铜元素与蛋白质结合，能够保护细胞促进红细胞生成[13]。对于病毒性心肌炎患者，铜离子水平波动不大，血清锌离子浓度较铜离子变化明显，因此铜锌比值增大。本研究结果显示阿魏酸钠联合双黄连注射液治疗的患者基质金属蛋白酶较单用阿魏酸钠治疗低，血清铜锌比值较小，提示双黄连注射液可能通过调节基质金属蛋白酶及铜锌水平发挥改善病毒性心肌炎心肌损伤的作用。

综上所述，阿魏酸钠联合双黄连注射液治疗病毒性心肌炎患者能够有效提高其临床疗效，可能与其显著降低血清基质金属蛋白酶及铜锌水平有关。

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