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瑞舒伐他汀与阿托伐他汀对冠心病高脂血症患者血脂及血浆 ADMA 水平的影响 *

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摘要 目的:探讨瑞舒伐他汀与阿托伐他汀对冠心病高脂血症患者血脂及血浆不对称二甲基精氨酸(ADMA)水平的影响。**方法:**选取 2016 年 3 月-2017 年 12 月四川大学华西医院收治的冠心病高脂血症患者 210 例为研究对象,随机分为研究组与对照组,每组各 105 例,研究组患者给予瑞舒伐他汀治疗,对照组给予阿托伐他汀治疗,均连续治疗 8 周。比较两组患者治疗前及治疗 8 周后血脂水平、ADMA 水平及血清炎症因子水平、血管内皮功能指标水平,记录两组患者的不良反应发生情况。**结果:**两组患者治疗前及治疗 8 周后甘油三酯(TG)、总胆固醇(TC)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)水平比较无统计学差异($P>0.05$),两组患者治疗 8 周后 TG、TC、LDL-C 水平均较治疗前降低($P<0.05$),而 HDL-C 水平与治疗前相比无统计学差异($P>0.05$)。两组患者治疗 8 周后 ADMA、超敏 C 反应蛋白(hs-CRP)、白介素-6(IL-6)水平均较治疗前降低,且研究组低于对照组($P<0.05$)。治疗 8 周后两组患者内皮素-1(ET-1)水平较治疗前降低,一氧化氮(NO)水平较治疗前升高($P<0.05$),且研究组患者 ET-1 水平低于对照组,NO 水平高于对照组($P<0.05$)。研究组与对照组患者在治疗期间均未发生难以耐受的不良反应。**结论:**与阿托伐他汀相比,应用瑞舒伐他汀治疗冠心病高脂血症患者可改善血管内皮功能和 TG、TC、LDL-C 水平,减轻炎症反应,降低 ADMA 水平,无严重不良反应发生,值得临床推广。

关键词:冠心病;高脂血症;瑞舒伐他汀;阿托伐他汀;血脂;不对称二甲基精氨酸

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Effects of Rosuvastatin and Atorvastatin on Blood Lipid and Plasma ADMA Levels in Patients with Hyperlipidemia in Coronary Heart Disease*

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ABSTRACT Objective: To investigate the effects of rosuvastatin and atorvastatin on blood lipid and plasma asymmetric two methyl arginine (ADMA) levels in patients with hyperlipidemia in coronary heart disease. **Methods:** A total of 210 patients with hyperlipidemia in coronary heart disease, who were treated in West China Hospital of Sichuan University from March 2016 to December 2017, were selected and were randomly divided into study group (n=105) and control group (n=105). The study group was treated with rosuvastatin and the control group was treated with atorvastatin for 8 weeks of continuous treatment. The levels of blood lipid, ADMA, serum inflammatory factors and vascular endothelial function were compared between the two groups before treatment and 8 weeks after treatment; the incidence of adverse reactions in the two groups was recorded. **Results:** There were no significant differences in the levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) between the two groups before treatment and 8 weeks after treatment ($P>0.05$). The levels of TG, TC and LDL-C of the two groups 8 weeks after treatment were lower than before treatment ($P<0.05$), but there was no statistical difference in HDL-C level compared with before treatment ($P>0.05$). The levels of ADMA, high sensitivity C reactive protein (hs-CRP) and interleukin-6 (IL-6) in the two groups 8 weeks after treatment were all lower than those before treatment, and the study group was lower than that in the control group ($P<0.05$). The level of endothelin-1 (ET-1) in the two groups 8 weeks after treatment was lower than that before treatment, and the level of nitric oxide (NO) was higher than that before treatment ($P<0.05$), and the level of ET-1 in the study group was lower than that of the control group, and the level of NO was higher than that of the control group ($P<0.05$). The patients in the two groups had no intolerant adverse reactions during the treatment. **Conclusion:** Compared with atorvastatin, the use of rosuvastatin in the patients with hyperlipidemia in coronary heart disease can improve vascular endothelial function, TG, TC and LDL-C levels, and it can reduce the

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inflammatory response and reduce the level of ADMA, without serious adverse reactions, which is worthy of clinical promotion.

Key words: Coronary heart disease; Hyperlipidemia; Rosuvastatin; Atorvastatin; Blood lipid; Asymmetric two methyl arginine

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前言

冠心病是临床常见的心血管疾病之一,高脂血症是冠心病患者常见的并发症,主要是指冠心病患者血浆中血脂水平过高^[1,2]。目前较多研究显示,炎症因子及血脂水平可有效反映冠心病高脂血症患者的病情变化^[3,4],同时不对称二甲基精氨酸(Asymmetric dimethyl arginine, ADMA)是反映血管内皮功能不全的标志物之一^[5,6],因此可通过检测冠心病高脂血症患者血脂及 ADMA 水平判断治疗效果。目前临床上治疗冠心病高脂血症患者主要应用他汀类药物,其可有效调节患者的血脂水平^[7,8]。然而,他汀类药物的种类较多,不同药物之间的治疗效果也存在一定的差异,瑞舒伐他汀与阿托伐他汀是临床常用于治疗高脂血症的降脂药物^[9,10],对调节血脂具有较好的疗效,但其对于冠心病高脂血症患者血浆 ADMA 水平影响的研究较少,因此本研究主要探讨瑞舒伐他汀与阿托伐他汀对冠心病高脂血症患者血脂及血浆 ADMA 水平的影响,旨在为临床治疗冠心病高脂血症提高参考依据,现作如下报道。

1 资料与方法

1.1 一般资料

选取 2016 年 3 月-2017 年 12 月期间四川大学华西医院收治的冠心病高脂血症患者 210 例为研究对象。纳入标准:(1)均符合全国第五届脑血管病学术会议《各类脑血管疾病的诊断要点》中冠心病高脂血症的相关诊断标准^[11];(2)4 周内未接受其他降脂类药物治疗者;(3)自愿参与本次研究,签署知情同意书者。排除标准:(1)伴有其他器质性心脏病者;(2)伴有恶性肿瘤者;(3)伴有肝肾功能障碍者;(4)伴有内分泌系统疾病者;(5)伴有精神性疾病者。将患者随机分为研究组与对照组,每组各 105 例。研究组男 64 例,女 41 例,年龄 47-82 岁,平均(67.32±10.39)岁,病程 1-7 年,平均(4.21±1.24)年。对照组男 62 例,女 43 例,年龄 49-81 岁,平均(68.65±11.42)岁,病程 1-9 年,平均病程(4.84±1.96)年。两组患者病程、年龄、性别比较无统计学差异($P>0.05$),本研究通过医院伦理委员会批准。

1.2 方法

所有受试者均给予改善心肌细胞代谢、抗血小板聚集、营养脑细胞及扩张冠状动脉血管等药物进行基础治疗。在此基础上对照组患者给予阿托伐他汀(辉瑞制药有限公司,国药准字 H20051407,规格:10 mg)治疗,20 mg/d,1 次/d,连续治疗 8 周,研究组患者给予瑞舒伐他汀(浙江京新药业股份有限公司,国药准字:H20080483,规格:10 mg)治疗,10 mg/次,1 次/d,连续治疗 8 周。

1.3 观察指标

在治疗前及治疗 8 周后抽取患者清晨空腹静脉血 10 mL,应用离心机(美国 Beckman 公司)以 3000 r/min 的转速离心 10 min,离心半径为 10 cm,将血清与血浆分离,应用日立 7086 型全自动生化分析仪检测患者血浆甘油三酯(Trilaurate glycerin, TG)、总胆固醇(Total cholesterol, TC)、高密度脂蛋白胆固醇(High density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(Low density lipoprotein cholesterol, LDL-C),试剂盒由日本和光工业株式会社提供,应用酶联免疫吸附法检测血清超敏 C 反应蛋白(Hypersensitive C reactive protein, hs-CRP)、白介素-6(Interleukin -6, IL-6)、血浆 ADMA 水平,应用放射免疫法检测内皮素-1(Endothelin-1, ET-1)水平,应用硝酸还原酶比色法检测一氧化氮(Nitric oxide, NO)水平,试剂盒由上海拜力生物科技有限公司提供,所有操作均严格按照试剂盒说明书进行。并观察两组患者的不良反应发生情况。

1.4 统计学方法

采用 SPSS19.0 统计学软件进行统计分析,计量资料以($\bar{x} \pm s$)的形式表示,经 t 检验处理,计数资料以%的形式表示,经 χ^2 检验处理,以 $P<0.05$ 时认为差异有统计学意义。

2 结果

2.1 两组患者血脂水平比较

两组患者治疗前及治疗 8 周后 TG、TC、HDL-C、LDL-C 水平比较无统计学差异($P>0.05$),两组患者治疗 8 周后 TG、TC、LDL-C 水平均较治疗前降低($P<0.05$),而 HDL-C 水平与治疗前相比无统计学差异($P>0.05$),见表 1。

表 1 两组患者血脂水平比较($\bar{x} \pm s$, mmol/L)

Table 1 Comparison of blood lipid levels between the two groups ($\bar{x} \pm s$, mmol/L)

Groups	n	TG		TC		HDL-C		LDL-C	
		Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment
Study group	105	2.32±0.81	1.54±0.31*	5.52±1.11	3.78±0.93*	1.16±0.27	1.24±0.32	3.78±1.01	2.29±0.67*
Control group	105	2.45±0.87	1.62±0.43*	5.47±1.09	3.84±0.96*	1.18±0.25	1.21±0.29	3.63±0.91	2.21±0.65*
t		1.121	1.546	0.329	0.460	0.557	0.712	1.131	0.878
P		0.264	0.124	0.742	0.646	0.578	0.477	0.260	0.381

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

2.2 两组患者 ADMA 水平及炎症因子水平比较 差异($P>0.05$),两组患者治疗 8 周后 ADMA、Hs-CRP、IL-6 水
两组患者治疗前 ADMA、Hs-CRP、IL-6 水平比较无统计学 平均较治疗前降低,且研究组低于对照组($P<0.05$),见表 2。

表 2 两组患者 ADMA 水平及炎症因子水平比较($\bar{x}\pm s$)
Table 2 Comparison of levels of ADMA and inflammatory factors between the two groups ($\bar{x}\pm s$)

Groups	n	ADMA($\mu\text{mol/L}$)		Hs-CRP(mg/L)		IL-6(ng/L)	
		Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment
Study group	105	3.51 $\pm$ 0.16	1.41 $\pm$ 0.12*	11.87 $\pm$ 3.15	2.89 $\pm$ 0.95*	15.29 $\pm$ 3.18	5.14 $\pm$ 0.78*
Control group	105	3.48 $\pm$ 0.13	2.56 $\pm$ 0.15*	12.54 $\pm$ 3.47	7.13 $\pm$ 1.27*	16.12 $\pm$ 3.25	10.42 $\pm$ 1.01*
t		1.491	11.345	1.465	9.378	1.870	8.973
P		0.137	0.000	0.144	0.000	0.063	0.000

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

2.3 两组患者血管内皮功能指标比较 较治疗前升高($P<0.05$),且研究组患者 ET-1 水平低于对照组,
两组患者治疗前 ET-1、NO 水平比较无统计学差异 ($P>0.05$),治疗 8 周后两组患者 ET-1 水平较治疗前降低,NO 水平
NO 水平高于对照组($P<0.05$),见表 3。

表 3 两组患者血管内皮功能指标比较($\bar{x}\pm s$)
Table 3 Comparison of vascular endothelial function between the two groups ($\bar{x}\pm s$)

Groups	n	ET-1(ng/L)		NO($\mu\text{mol/L}$)	
		Before treatment	8 weeks after treatment	Before treatment	8 weeks after treatment
Study group	105	89.25 $\pm$ 9.73	52.65 $\pm$ 7.87*	48.35 $\pm$ 6.64	73.92 $\pm$ 7.13*
Control group	105	91.19 $\pm$ 10.14	73.86 $\pm$ 8.43*	47.21 $\pm$ 6.58	58.32 $\pm$ 7.59*
t		1.415	9.331	1.031	8.236
P		0.159	0.000	0.312	0.000

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

2.4 安全性分析

研究组与对照组患者在治疗期间均未发生难以耐受的不良反应。

3 讨论

冠心病的本质为冠状动脉粥样硬化,大多数患者是由于血管内皮炎症反应及脂质堆积而引发^[12]。近年来,有研究显示,高脂血症是冠心病患者引发心血管事件的重要因素之一,分析其原因可能是血液中脂质代谢发生异常,导致冠脉的直径减小,使患者心肌缺血状态加重,高脂血症可减少血管内皮细胞分泌血管内皮生长因子,同时还能诱导氧化应激损伤、局部炎症反应,最终导致斑块破裂及血管腔狭窄等^[13-15]。因此积极控制冠心病高脂血症患者的血脂水平,抑制炎症反应,对阻止病情进一步发展具有重要的临床意义。他汀类药物是心血管疾病常用的抗炎、降脂药物,能够有效的保护血管内皮细胞,并具有扩张血管的作用^[16,17]。阿托伐他汀对调节血脂的疗效已经在临床上得到证实,常被应用于冠心病高脂血症的治疗^[18,19]。瑞舒伐他汀是一种新型的他汀类药物,其可通过抑制羟甲基戊二酰辅酶 A 还原酶的合成,使血浆 TC、LDL-C、TG 水平降低,并能使患者 HDL-C 水平升高,进而达到调节血脂的作用,同时还能够抑制血管炎症反应,降低心血管事件的发生率^[20-22]。

本研究结果显示,两组患者治疗 8 周后 TG、TC、LDL-C 水

平均较治疗前降低($P<0.05$),而 HDL-C 水平与治疗前相比无统计学差异 ($P>0.05$),但两组患者治疗前及治疗 8 周后 TG、TC、HDL-C、LDL-C 水平比较无统计学差异($P>0.05$),说明阿托伐他汀与瑞舒伐他汀的降脂效果相当。Hs-CRP 是机体非特异性炎症反应的标志物之一,能够准确的反映冠心病患者炎症反应水平^[23];IL-6 是一种促炎性因子,由免疫细胞产生,并能促进 Hs-CRP 的产生,两者均在动脉粥样硬化的发生发展中发挥重要作用^[24]。ADMA 是一种左旋精氨酸类似物,主要由血管内皮细胞合成与释放,可减少 NO 的合成,进而引发血管内皮功能障碍^[25]。本研究结果还显示,两组患者治疗 8 周后 ADMA、Hs-CRP、IL-6 水平均较治疗前降低,且研究组低于对照组($P<0.05$),说明瑞舒伐他汀能够更有效的控制冠心病高脂血症患者的炎症反应及降低血浆 ADMA 水平,分析其原因可能是因为瑞舒伐他汀的半衰期较阿托伐他汀长,且不通过 P540 酶系代谢,具有较高的生物利用率,药效高于阿托伐他汀,同时瑞舒伐他汀可通过免疫调节来抑制炎症反应,还可通过增加单核细胞过氧化物酶体增殖激活受体的表达,减轻炎症反应,使 Hs-CRP、IL-6 水平进一步降低^[26,27]。ADMA 主要是由血管内皮细胞分泌的,可通过二甲基精氨酸二甲氨水解酶水解成单甲胺、二甲胺及瓜氨酸,当二甲基精氨酸二甲氨水解酶失活时,可导 ADMA 在患者体内的水平升高,而高脂血症可致使二甲基精氨酸二甲氨水解酶失活,进而促使 ADMA 的水平升高,瑞舒

伐他汀具有调节血浆血脂水平的作用,推测瑞舒伐他汀可能是通过下调血脂水平来恢复二甲基精氨酸二甲氨水解酶的活性,进而使 ADMA 水平降低^[28]。此外,治疗 8 周后两组患者 ET-1 水平较治疗前降低,NO 水平较治疗前升高 ($P<0.05$),且研究组患者 ET-1 水平低于对照组,NO 水平高于对照组 ($P<0.05$),说明 ET-1、NO 与冠心病的发生具有密切相关性。ET-1、NO 均是反应血管内皮细胞功能的敏感指标,均由血管内皮细胞分泌,其中 ET-1 对 NO 具有拮抗作用,能够有效的收缩血管,促进平滑肌增殖及白细胞黏附,在动脉粥样硬化的发生中发挥着重要作用,NO 具有舒张血管的作用,同时还能够抑制平滑肌增殖及白细胞黏附,对动脉粥样硬化的发展具有抑制作用^[29,30]。两组患者在治疗期间均未发生难以耐受的不良反应,说明瑞舒伐他汀与阿托伐他汀治疗冠心病高脂血症均具有较高的安全性。

综上所述,瑞舒伐他汀与阿托伐他汀治疗冠心病高脂血症均具有调节血脂、减轻炎症反应、改善 ADMA 水平及血管内皮功能的作用,其中瑞舒伐他汀对减轻炎症反应、改善 ADMA 水平及血管内皮功能的效果更显著,同时两种药物均具有较高的安全性,在临床治疗过程中应切合患者病情选择合适的治疗药物。

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