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瑞舒伐他汀钙与非诺贝特联合治疗血脂异常的疗效及对肝肾功能的影响 *

杜 婧 邓雁北 高 颖 项晓燕 李文亚

(上海交通大学医学院附属苏州九龙医院内分泌与代谢科 江苏 苏州 215028)

摘要 目的:观察瑞舒伐他汀钙与非诺贝特联合治疗血脂异常的疗效及对肝肾功能的影响。**方法:**选择2017年1月至2019年6月间我院门诊收治的127例血脂异常患者,随机分为研究组($n=63$)和对照组($n=64$),在针对合并症给予对症治疗的基础上,对照组采用瑞舒伐他汀钙治疗,研究组在对照组基础上联合非诺贝特治疗。观察两组血脂水平、肝肾功能、临床效果以及不良反应发生率。**结果:**治疗后,两组总胆固醇(TC)、低密度脂蛋白胆固醇(LDL-C)、甘油三酯(TG)水平低于治疗前($P<0.05$),且研究组低于对照组($P<0.05$);高密度脂蛋白胆固醇(HDL-C)、丙氨酸氨基转移酶(ALT)水平均高于治疗前($P<0.05$),且研究组高于对照组($P<0.05$);两组治疗前后尿素氮(UN)、肌酐(Cr)比较差异无统计学意义($P>0.05$);研究组的总有效率为92.06%(58/63),高于对照组的79.69%(51/64),差异有统计学意义($P<0.05$);研究组不良反应发生率为11.11%(7/63),稍高于对照组的9.38%(6/64),但差异无统计学意义($P>0.05$)。**结论:**在瑞舒伐他汀钙基础上联合非诺贝特治疗血脂异常可提高临床有效率,可增强调节血脂的作用,其安全性较好,但对血脂异常患者的肝功能影响较大,临床可视患者情况合理选用用药方案。

关键词:瑞舒伐他汀钙;非诺贝特;血脂异常;肝功能;肾功能;不良反应

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Effect of Rosuvastatin Calcium Combined with Fenofibrate in the Treatment of Dyslipidemia and Its Effect on Liver and Renal Function*

DU Jing, DENG Yan-bei, GAO Ying, XIANG Xiao-yan, LI Wen-ya

(Department of Endocrinology and Metabolism, Suzhou Jiulong Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Suzhou, Jiangsu, 215028, China)

ABSTRACT Objective: To observe the clinical effects of rosuvastatin calcium combined with fenofibrate therapy on dyslipidemia and its effect on liver and renal function. **Methods:** 127 patients with dyslipidemia in outpatient department of our hospital from January 2017 to June 2019 were selected, which were divided into study group($n=63$) and control group($n=64$) according to random number table method, the control group was treated with rosuvastatin calcium on the basis of symptomatic treatment for the complications, the study group was treated with fenofibrate on the basis of control group. Blood lipid levels, liver and renal function, clinical effect and adverse reaction rate of the two groups were observed. **Results:** After the treatment, the levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triacylglycerol (TG) were significantly lower than those before treatment ($P<0.05$), which in the study group were significantly lower than in the control group ($P<0.05$); High density lipoprotein cholesterol (HDL-C) and alanine transferase (ALT) were significantly higher than that before treatment ($P<0.05$), which in the study group were significantly higher than the control group ($P<0.05$); There were no significant difference in the levels of urea nitrogen (UN) and creatinine (Cr)($P>0.05$); The total effective rate of the study group was 92.06%(58/63), significantly higher than that in the control group of 79.69%(51/64), the difference was statistically significant ($P<0.05$); The incidence rate of adverse reactions was 11.11%(7/63) in the study group, slightly higher than that of the control group of 9.38%(6/64), while the difference was not statistically significant ($P>0.05$). **Conclusion:** On the basis of rosuvastatin calcium combined with fenofibrate in the treatment of dyslipidemia can improve the clinical efficiency, enhance the role of regulating blood lipid, its safety is better, but it has a greater impact on the liver function of patients with dyslipidemia, and the clinical use of drugs can be reasonable according to the situation of patients.

Key words: Rosuvastatin calcium; Fenofibrate; Dyslipidemia; Liver function; Renal function; Adverse reactions

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前言

血脂异常属于临床常见疾病,由于该病患者血脂长期处于较高水平状态,可随着病情发展诱发颈动脉或冠状动脉粥样硬化

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作者简介:杜婧(1982-),女,博士,副主任医师,研究方向:内分泌与代谢疾病, E-mail: du_lilian@163.com

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化及胰腺炎等^[1-3],因此可对患者的生活质量带来重大威胁。此种疾病多由脂肪代谢异常所致,主要表现为高胆固醇血症、高甘油三酯血症。近年来,其发病率呈上升趋势,且多见于中老年人,若治疗不及时可诱发心脑血管疾病,将持续加重我国医疗的负担^[4]。目前临床治疗该病主要采用他汀类药物,可在一定程度上改善血脂水平,但作用靶点单一,整体治疗效果不理想^[5]。非诺贝特具有良好的降脂作用,口服后 4-7 小时内即可发挥较好的降脂作用^[6,7],为探究更为安全高效的治疗方案,本研究将瑞舒伐他汀钙联合非诺贝特的联合用药方案用于治疗血脂异常患者,取得了较为满意的结果,现报告如下。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月至 2019 年 6 月我院门诊收治的血脂异常患者 127 例。纳入标准:① 符合《中国成人血脂异常防治指南》(2016 年修订版)^[8]中关于血脂异常的诊断标准;② 患者对本研究知情并签署了知情同意书;③ 近 1 个月内未进行调脂治疗。排除标准:① 依从性差,无法配合本研究者;② 对本次研究所使用药物过敏者;③ 严重肝、肾等重要脏器功能不全者。随机分为研究组($n=63$)和对照组($n=64$),其中研究组男 39 例,女 24 例,年龄 39~68 岁,平均(52.48 ± 10.24)岁,合并高血压、糖尿病、冠心病分别为 14 例、6 例、7 例;对照组男 37 例,女 27 例,年龄 35~67 岁,平均(52.35 ± 10.29)岁,合并高血压、糖尿病、冠心病分别为 13 例、7 例、7 例。两组一般资料对比无差异($P>0.05$),具有可比性。

1.2 用药方案

给予合并高血压、糖尿病、冠心病的血脂异常患者对症治疗,在此基础上,对照组用药方案:瑞舒伐他汀钙片(阿斯利康药业(中国)有限公司,规格:10 mg,国药准字 J20160025),口服,每次 10 mg,1 天 1 次,共治疗 10 周。① 研究组:在对照组基

础上联合非诺贝特胶囊(ABBOTT LABORATORIES LIMITED,规格:0.2 g,进口药品注册证号 H20160155)治疗:口服,每次 0.2 g,1 天 1 次,共治疗 10 周。

1.3 观察指标

1.3.1 血脂及肝功能指标的检测 分别于治疗前、治疗后于清晨抽取患者肘部静脉血 3-5 mL,采用酶法检测患者血脂水平,包括总胆固醇(Total Cholesterol,TC)、高密度脂蛋白胆固醇(High Density Lipoprotein Cholesterol,HDL-C)、甘油三酯(Triacylglycerol,TG)、低密度脂蛋白胆固醇(Low Density Lipoprotein Cholesterol,LDL-C);比色法检测丙氨酸氨基转移酶(Alanine Transferase,ALT)、尿素氮(Urea Nitrogen,UN)、肌酐(Creatinine,Cr)水平(罗氏公司 COBAS C501 全自动生化分析仪)。

1.3.2 不良反应发生情况 观察治疗期间患者是否出现肝功能异常、恶心、肌痛、皮肤瘙痒以及便秘等不良反应。

1.3.3 疗效评价 显效:TC 下降幅度超过 20%或 LDL-C 下降幅度在 20%以上或 HDL-C 水平升高在 0.26 mmol/L 以上;有效:TC 下降幅度在 10~20%或 LDL-C 下降幅度在 10~20%或 HDL-C 水平升高在 0.10~0.25 mmol/L 之间;无效:未达到上述标准。总有效 = 显效 + 有效^[9]。

1.4 统计学处理

采用 SPSS25.0 统计学软件进行统计分析,计数资料均用例或者百分率(%)表示,用 检验;计量资料用($\bar{x} \pm s$)表示,用 t 检验,当 $P<0.05$ 时表示差异具有统计学意义。

2 结果

2.1 血脂水平比较

治疗前两组 TC、LDL-C、HDL-C、TG 水平比较无差异($P>0.05$),治疗后两组 TC、LDL-C、TG 水平低于治疗前($P<0.05$),且研究组低于对照组($P<0.05$),HDL-C 水平高于治疗前($P<0.05$),且研究组显著高于对照组($P<0.05$),详见表 1。

表 1 两组血脂各项指标比较($\bar{x} \pm s$)

Table 1 Comparison of blood lipid indexes between the two groups($\bar{x} \pm s$)

Groups	n	TC(mmol/L)		LDL-C(mmol/L)		TG(mmol/L)		HDL-C(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research Group	63	6.98 $\pm$ 1.14	4.36 $\pm$ 1.12*	4.73 $\pm$ 0.58	3.24 $\pm$ 0.17*	3.64 $\pm$ 0.21	2.16 $\pm$ 0.13*	1.16 $\pm$ 0.23	1.85 $\pm$ 0.34*
Control group	64	7.02 $\pm$ 1.25	5.28 $\pm$ 1.02*	4.67 $\pm$ 0.54	3.96 $\pm$ 0.27*	3.68 $\pm$ 0.22	2.69 $\pm$ 0.25*	1.12 $\pm$ 0.24	1.42 $\pm$ 0.29*
t		0.188	4.481	0.603	17.951	1.048	14.954	0.959	7.672
P		0.851	0.000	0.547	0.000	0.297	0.000	0.340	0.000

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

2.2 肝肾功能比较

治疗前两组 ALT、UN、Cr 比较差异无统计学意义($P>0.05$),治疗后两组 ALT 均高于治疗前($P<0.05$),且研究组高于对照组($P<0.05$);治疗前后两组 UN、Cr 比较差异无统计学意义($P>0.05$),详见表 2。

2.3 临床疗效比较

研究组的总有效率为 92.06%(58/63),高于对照组的 79.69%(51/64),差异有统计学意义($P<0.05$),详见表 3。

2.4 不良反应发生率

研究组出现肝功能异常、恶心、便秘分别为 1 例、3 例、3 例,不良反应发生率为 11.11%(7/63);对照组出现皮肤瘙痒、恶心、肌痛分别为 2 例、2 例、2 例,不良反应发生率为 9.38%(6/64),差异无统计学意义($\chi^2=0.104$, $P=0.747$)。

3 讨论

血脂异常是导致冠心病、动脉粥样硬化和脑血管疾病的主

要因素,目前研究已发现与血脂异常有关的因素很多,如肝脏疾病、糖尿病、肥胖均与血脂异常相关^[10-12]。当前已有研究证实血脂异常患者动脉粥样硬化性心血管疾病的危险因素,而血脂

异常的治疗以控制血脂为主^[13],因此如何选择合理的调脂用药方案成为当前血脂异常研究的重点之一。

表 2 两组肝肾功能比较($\bar{x} \pm s$)Table 2 Comparison of liver and kidney function between the two groups($\bar{x} \pm s$)

Groups	n	ALT(U/L)		UN(mmol/L)		Cr(μ mol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research Group	63	42.36 $\pm$ 3.28	56.19 $\pm$ 2.26*	4.56 $\pm$ 1.03	4.62 $\pm$ 1.23	69.78 $\pm$ 10.34	70.74 $\pm$ 10.38
Control group	64	42.52 $\pm$ 3.14	49.24 $\pm$ 3.21*	4.51 $\pm$ 1.14	4.55 $\pm$ 1.26	70.21 $\pm$ 10.42	71.46 $\pm$ 10.35
t		0.281	14.088	0.259	0.333	0.233	0.391
P		0.799	0.000	0.796	0.740	0.816	0.696

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

表 3 两组临床疗效比较 [n(%)]

Table 3 Comparison of clinical efficacy between the two groups[n(%)]

Groups	n	Markedly effective	Effective	Invalid	Total effective
Research Group	63	25(39.68)	33(52.38)	5(7.94)	58(92.06)
Control group	64	20(31.25)	31(48.44)	13(20.31)	51(79.69)
χ^2					3.997
P					0.046

本研究中采用两种治疗方案后,血脂指标水平均得到一定改善,且联合治疗效果更佳,这是因为瑞舒伐他汀钙作为临床治疗血脂异常常用药物,是羟甲基戊二酰单酰辅酶 A(Hydroxy-Methyl-Glutaryl Coenzyme A, HMG-CoA) 还原酶抑制剂,能够有效抑制胆固醇合成,从而降低 TC、LDL-C 水平,并能提高 HDL-C 水平,进而起到调节血脂的作用^[14-16]。但该药物作用靶点单一,单纯使用整体疗效不理想^[17]。非诺贝特属于第三代氯贝丁酯类药物,其在体内的代谢产物非诺贝特酸可降低 TG 水平,并能提高 HDL-C 水平^[18],其主要作用机制是通过对腺苷酸环化酶进行抑制,进而减少细胞中环腺苷酸含量^[19],还可抑制脂肪组织水解,有效减少非酯化脂肪酸含量,进而减少极低密度脂蛋白(Very Low Density Lipoprotein, VLDL)分泌,进而发挥调脂作用^[20-22]。既往研究显示非诺贝特能够有效提高脂蛋白酶活性,促使 VLDL 发生水解,进而降低其在血液中浓度从而发挥降脂作用^[23]。非诺贝特还可促进 TG 与 HDL 中胆固醇可的交换,进而提高 HDL 浓度^[24,25]。另外还有研究表明^[26],非诺贝特还可以通过激活氧化物酶增殖体激活型受体 α (PPAR- α),从而促进脂蛋白酶和载脂蛋白 A1 以及清道夫受体 B 类 1 型等物质的合成,从而达到调节血脂的作用。瑞舒伐他汀钙与非诺贝特作用机制不同,瑞舒伐他汀钙降胆固醇效果较好,而非诺贝特可有效降低 TG 水平^[27],二者联合使用可充分发挥互补作用,可以达到降压、调脂,全面改善血脂水平,提高临床治疗效果。

有研究表明^[28],采用瑞舒伐他汀钙与非诺贝特治疗血脂异常,患者血脂水平得到显著改善。此外本研中两组肾功能各项指标治疗前、后无显著变化,但肝功能指标 ALT 升高,研究组患者 ALT 水平更高,提示两种方案均会对患者肝功能造成一定损伤,且联合用药对肝功能损伤更大,既往已有研究指出非

诺贝特和瑞舒伐他汀钙均会影响肝肾功能^[29],而本研究中尚未发现两种用药方案对肾功能的不利影响,这可能是研究中用药剂量得到合理控制,且未长期服药所致。另研究组不良反应发生率稍高于对照组,提示采用瑞舒伐他汀钙与非诺贝特治疗血脂异常时应根注意对于肝肾功能不全以及身体素质相对较差的患者应合理使用,以提高临床药物应用的安全性和合理性^[30]。

综上所述,采用瑞舒伐他汀钙与非诺贝特治疗血脂异常,可有效改善患者血脂水平,提高临床治疗效果,但鉴于研究中发现其对肝功能的损害较大,临床应根据实际情况,避免对肝功能不全的血脂异常患者使用,以保证临床药物应用的合理性。

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