

格列吡嗪合并辛伐他汀对颈动脉粥样硬化斑块的疗效观察

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摘要 目的:研究辛伐他汀对治疗并发高脂血症的颈动脉粥样硬化斑块的影响,以及合用格列吡嗪对辛伐他汀的增效作用。**方法:**将高脂血症并发颈动脉粥样硬化患者 108 例,随机分为 2 组,辛伐他汀治疗组和格列吡嗪合并辛伐他汀治疗组,6 个月治疗后,测量血脂生化指标、炎症因子活性和高频彩色多普勒超声内-中膜厚度(IMT)。**结果:**两个治疗组,治疗后与治疗前相比,血脂指标,炎症因子指标及其 IMT 值都具有显著性差异($P<0.05$)。与辛伐他汀单独治疗相比,格列吡嗪合并辛伐他汀治疗组的 TC、TG 和 HDL-C 没有显著性差异($P>0.05$),但 LDL-C 显著减少($P<0.05$),两组间 ET-1 和 TNF- α 以及 IMT 值差异显著($P<0.05$)。**结论:**辛伐他汀能够改善血脂水平,降低炎症因子活性,进而对颈动脉粥样硬化具有治疗作用,而合并格列吡嗪治疗能够起到增效作用。

关键词 格列吡嗪 辛伐他汀 血脂 炎症因子 内膜-中膜厚度 动脉粥样硬化

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Therapeutic Efficacy of Simvastatin plus Glipizide in Patients with Carotid Atherosclerotic Plaques

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ABSTRACT Objective: To evaluate the therapeutic efficacy of simvastatin in patients with carotid atherosclerotic plaques complicated with hyperlipidemia, and the synergistic effect of glipizide. **Methods:** All the 108 patients were divided into two groups: group treatment with simvastatin and group treatment with simvastatin and glipizide. After treatment for 6 months, we measured the biochemical indicator of blood fat, included TC, TG, LDL-C and HDL-C, the activity of inflammatory factors, included ET-1 and TNF- α , and the intima-media thickness (IMT). **Results:** Both of the 2 groups, the scores of biochemical indicator of blood lipids, activity of inflammatory factors and intima-media thickness (IMT) were changed significantly after treatment ($P<0.05$). Compared with group treatment with simvastatin, the changes of the scores of TC, TG and HDL-C were not significant ($P>0.05$). However, the scores of LDL-C, activity of inflammatory factors and IMT were decreased significantly ($P<0.05$). **Conclusion:** Simvastatin could improve carotid atherosclerosis, through improving the level of blood lipids and reducing the activity of inflammatory factors, and glipizide had a synergistic effect.

Key words: Glipizide; Simvastatin; Blood lipids; Inflammatory factors; Intima-media thickness (IMT); Atherosclerosis

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前言

动脉粥样硬化(AS)是一种以动脉壁脂质蓄积为特征的复杂病变过程,是引起心脑血管疾病的首要原因。一些研究表明颈动脉粥样硬化与急性心肌梗死或脑梗死的发生率相关显著^[1-3]。所以颈动脉粥样硬化作为无创性检查预测心脑血管事件发生在临床上逐渐得到应用。格列吡嗪为第二代磺脲类口服降血糖药。有关研究发现,其可改善高脂血症,降低甘油三酯和胆固醇水平,提高高密度脂蛋白胆固醇在总胆固醇中比率,还可抑制血小板聚集和促进纤维蛋白溶解,因而对血管病变可能有一定的防治作用^[4-5]。他汀类药物治疗心血管疾病的疗效已得到公认^[6-8]。本研究通过应用血脂生化指标检测、炎症因子活性测定和高频彩色多普勒超声,观察辛伐他汀对治疗并发高脂血症的动脉粥样硬化斑块的影响,以及合用格列吡嗪对辛伐他汀的增效作用。

1 资料和方法

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1.1 临床资料

连续入选 2009 年 6 月-2010 年 6 月期间,高脂血症并发颈动脉粥样硬化患者 108 例,男 58 例,女 50 例,年龄 54 岁~67 岁(60.3 ± 7.3 岁)。随机分为 2 组,辛伐他汀组 54 例,男 29 例,女 25 例,年龄 54 岁~67 岁(60.9 ± 7.8 岁);合并高血压 24 例,合并糖尿病 11 例。辛伐他汀+格列吡嗪组 54 例,男 29 例,女 25 例,年龄 54 岁~66 岁(60.6 ± 7.1 岁);合并高血压 25 例,合并糖尿病 13 例。2 组性别、年龄和并发症均无统计学差异($P>0.05$)。

1.2 治疗方法

辛伐他汀组,患者每日睡前顿服辛伐他汀片 20mg(默沙东中国有限公司)。格列吡嗪+辛伐他汀组,患者每日顿服辛伐他汀片 20mg 格列吡嗪(威海迪沙药业有限公司),2.5mg,一日三次,口服。疗程为 6 个月。

1.3 血脂生化检测

所有患者抽血前 3 天禁高脂饮食,12 h 禁食取静脉血,采用自动生化仪测定血清总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)和高密度脂蛋白胆固醇(HDL-C)。

1.4 ET-1 和 TNF- α 测定

ET-1 的测定,患者的标本均为晨起空腹静脉血,采血 4 ml

注入含 10%的 EDTA 30 μ l 和抑肽酶 40 μ l 的塑料管中,用放射免疫法测定血浆 ET-1 水平。TNF- α 的测量,静脉血 4 ml 放入普通试管内,室温下放置 1 h,1 500 r/min 离心,分离出血清,-20 $^{\circ}$ C 冰箱储存备用。用放免法测定 TNF- α 含量,试剂盒由长沙贝泰生物科技有限公司提供。

1.5 颈动脉超声测量

治疗前后采用彩色多普勒超声,分别测量两侧颈动脉(CCA)、颈内动脉(ICA)、颈外动脉(ECA)各斑块厚度。斑块厚度为内膜-动脉腔界面至中外膜界面的距离,以后壁为标准,内-中膜厚度(IMT)>1.0 mm 即称为动脉粥样硬化斑块增厚。测 CCA、ICA、ECA 粥样硬化斑块最厚处和最薄处,冻结颈动脉窦下 1.0cm 的图像同一位置分别测量 3 次,取平均值为颈动脉内膜厚度。

1.6 统计学处理

数据采用 SPSS13.0 进行独立样本 T 检验统计分析,数据结果,以 P<0.05 表示有统计学意义;多个样本间的多重比较采用 ANOVA (SNK-q 与 LSD-) 统计分析,以 P<0.05 表示有统计学意义。

2 结果

2.1 病例完成情况

本研究所选 108 例患者无失访病例,全部完成预定研究疗程,且两组患者基线水平差异没有统计学意义。

2.2 两治疗组血脂变化结果

两组治疗后较治疗前血清 TC、TG、LDL-C 和 HDL-C 具有好转 (P<0.05),而治疗后两组之间,同辛伐他汀组相比,格列吡嗪+辛伐他汀组 LDL-C 显著好转 (P<0.05),而其它 TC、TG 和 HDL-C 无统计学差异 (P>0.05)。详见表 1。

表 1 治疗前后血脂生化指标 ($\bar{x} \pm s$) 单位 mmol/L
Table 1 Outcomes of blood lipids ($\bar{x} \pm s$) mmol/L

Group		TC	TG	LDL-C	HDL-C
S	Prior treatment	5.79 $\pm$ 0.64	1.92 $\pm$ 0.71	3.89 $\pm$ 0.35	1.03 $\pm$ 0.21
	After treatment	4.33 $\pm$ 0.64*	1.24 $\pm$ 0.41*	2.41 $\pm$ 0.63*	1.37 $\pm$ 0.20*
G+ S	Prior treatment	5.61 $\pm$ 0.72	1.84 $\pm$ 0.75	3.42 $\pm$ 0.65	1.17 $\pm$ 0.22
	After treatment	4.13 $\pm$ 0.62*	1.12 $\pm$ 0.51*	1.87 $\pm$ 0.69* Δ	1.62 $\pm$ 0.23*

注 S- 辛伐他汀单独治疗 G+S- 格列吡嗪+辛伐他汀 ;*P<0.05 vs 治疗前, Δ P<0.05 vs 辛伐他汀单独治疗后。

Note S-treatment with simvastatin lonely G+ S-treatment with glipizide plus simvastatin ; *P<0.05 vs prior treatment, Δ P<0.05 vs after treatment with simvastatin lonely.

2.3 EP-1 和 TNF- α 测定结果

两治疗组,在治疗后 EP-1 和 TNF- α 治疗后都显著减少 (两治疗组,在治疗后 EP-1 和 TNF- α 治疗后都显著减少 (P<0.

05)。同辛伐他汀单独治疗组相比,格列吡嗪+辛伐他汀治疗组治疗后,EP-1 和 TNF- α 都显著减少 (P<0.05)。详见表 2。

表 2 EP-1 和 TNF- α 测定结果 ($\bar{x} \pm s$)
Table 2 Outcomes of EP-1 and TNF- α ($\bar{x} \pm s$)

Group		ET-1(ng/L)	TNF- α (ng/L)
S	Prior treatment	69.08 $\pm$ 10.12	0.329 $\pm$ 0.033
	After treatment	58.93 $\pm$ 8.15*	0.240 $\pm$ 0.031*
G+ S	Prior treatment	68.73 $\pm$ 10.26	0.336 $\pm$ 0.042
	After treatment	53.65 $\pm$ 9.62* Δ	0.207 $\pm$ 0.037* Δ

注 S- 辛伐他汀单独治疗 G+S- 格列吡嗪+辛伐他汀 ;*P<0.05 vs 治疗前, Δ P<0.05 vs 辛伐他汀单独治疗后。

Note S-treatment with simvastatin lonely G+ S-treatment with glipizide plus simvastatin ; *P<0.05 vs prior treatment, Δ P<0.05 vs after treatment with simvastatin lonely.

表 3 两组治疗前后 IMT 值 ($\bar{x} \pm s$)
Table 3 Outcomes of IMT ($\bar{x} \pm s$)

Group		IMT(mm)
S	Prior treatment	1.251 $\pm$ 0.132
	After treatment	0.963 $\pm$ 0.124*
G+ S	Prior treatment	1.248 $\pm$ 0.143
	After treatment	0.829 $\pm$ 0.117* Δ

注 S- 辛伐他汀单独治疗 G+S- 格列吡嗪+辛伐他汀 ;*P<0.05 vs 治疗前, Δ P<0.05 vs 辛伐他汀单独治疗后。

Note S-treatment with simvastatin lonely G+ S-treatment with glipizide plus simvastatin ; *P<0.05 vs prior treatment, Δ P<0.05 vs after treatment with simvastatin lonely.

3 讨论

以往研究表明,低密度脂蛋白受体 (LDLR) 和高密度脂蛋白受体 (HDLR) 等基因突变等导致的血脂过多以及血管炎症损伤,是重要的动脉粥样硬化病理机制^[9-11]。动脉粥样硬化的局部病变有动脉内膜增厚及纤维斑块的形成,IMT 的改变早于斑块的发生,所以颈动脉 IMT 增厚是一种早期反映动脉粥样硬化的无创性指标,其改变早于斑块的发生。大量的研究认为,颈动脉 IMT 不仅能反映颈动脉局部的动脉粥样硬化进展情况,也是全身动脉粥样硬化的早期评价指标^[1-3]。所以我们以血浆血脂检测、炎症因子 EP-1 和 TNF- α 以及 IMT 作为检测两组药物治疗效果的指标。

辛伐他汀为甲基羟物乙酰辅酶 A(HMG-CoA)还原酶抑制剂,其降血脂原理为抑制 HMG-CoA、减少细胞内胆固醇的生物合成;增加细胞表面低密度脂蛋白受体,加速体内胆固醇代谢,加强脂蛋白解酶的活性,降低甘油三酯浓度,进而起到动脉粥样硬化的治疗作用^[2, 12-13]。同时,他汀类药物也能够通过抑制 ET-1 和 TNF- α 等细胞炎症因子的活性,来抑制动脉粥样硬化斑块的形成^[14-15]。而格列吡嗪作为第二代磺脲类口服降血糖药,有关研究发现,其可改善高脂血症,降低甘油三酯和胆固醇水平,同时对 TNF- α 等炎症因子的表达也有抑制作用^[4-5]。所以,我们通过临床病例研究去证明,格列吡嗪合并辛伐他汀治疗是否起到增效作用。

我们的研究结果显示,两个治疗组,6 个月治疗后,血脂指标,炎症因子指标及其 IMT 值都得到改善。虽然同辛伐他汀单独治疗相比,格列吡嗪合并辛伐他汀治疗组的 TC、TG 和 HDL-C 没有显著性差异,但 LDL-C 显著减少,仍然说明格列吡嗪合并辛伐他汀治疗能够更有效的改善血脂。两组间 ET-1 和 IMT 值的比较则更明确的说明,合并治疗更能够降低炎症因子表达,减轻经动脉粥样硬化斑块发生发展。

综上所述,我们的研究表明,格列吡嗪合并辛伐他汀治疗能够更有效的改善血脂水平,降低炎症因子表达,进而对高血脂症并发经动脉粥样硬化起到更有效的治疗作用。

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