·临床研究·

# 阿托伐他汀对动脉粥样硬化性脑梗死患者的调脂效果及颈动脉粥样硬化斑块的影响

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【摘要】 **目的** 分析阿托伐他汀对动脉粥样硬化性脑梗死患者的调脂效果及对颈动脉粥样硬化斑块的影响。**方法** 92例动脉粥样硬化性脑梗死患者采用随机数字表法随机分为阿托伐他汀(20 mg/d)治疗组和非他汀类药物治疗组(对照组),评价两组患者治疗前后血脂水平和颈动脉斑块变化。**结果** 经阿托伐他汀治疗后,阿托伐他汀组患者血清总胆固醇、甘油三酯、低密度脂蛋白胆固醇水平降低(均$P<0.05$),高密度脂蛋白胆固醇水平升高($P<0.05$);颈动脉斑块面积、斑块厚度和颈动脉内-中膜厚度明显改善(均$P<0.05$)。**结论** 阿托伐他汀具有改善动脉粥样硬化性脑梗死患者血脂水平、软化甚至缩小颈动脉斑块作用,有利于脑梗死患者的二级预防且无明显不良反应。

【关键词】 脑梗死; 动脉粥样硬化; 降血脂药

## The effect of lipid regulation with atorvastatin on the blood lipid levels and carotid artery plaques in patients with atherosclerotic cerebral infarction

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【**Abstract**】 **Objective** To analyze the effect of intensive lipid regulation treatment with atorvastatin on the blood lipid levels and carotid artery plaques in patients with atherosclerotic cerebral infarction. **Methods** Ninety-two patients with atherosclerotic cerebral infarction were randomly divided into two groups: observation group (treated by atorvastatin calcium with the dosage of 20 mg/d, N = 46) and control group (treated by diet without lipid-rich food, N=46). Besides, other drugs given to the patients in two groups were the same. The blood lipid levels and the changes of carotid artery plaques in two groups were analyzed and compared before treatment and 3 months after treatment. **Results** After treatment, the concentrations of total cholesterol [TC, (4.23 ± 0.92) mmol/L vs (5.24 ± 0.68) mmol/L], triglyceride [TG, (2.46 ± 0.28) mmol/L vs (3.33 ± 0.47) mmol/L], low-density lipoprotein cholesterol [LDL-C, (2.52 ± 0.38) mmol/L vs (4.78 ± 0.86) mmol/L] in the patients of observation group were all decreased and significantly lower than those in the control group ($P = 0.000$, for all), and the concentration of high-density lipoprotein cholesterol [HDL-C, (1.13 ± 0.41) mmol/L vs (0.85 ± 0.32) mmol/L] in the patients of observation group was increased and significantly than that in the control group ($P = 0.003$). The carotid artery plaque size [(20.25 ± 0.32) $mm^2$ vs (24.42 ± 10.33) $mm^2$] and thickness [(0.59 ± 0.13) mm vs (1.93 ± 0.23) mm] of carotid artery plaques and intima-media thickness [IMT, (1.32 ± 0.67) mm vs (1.63 ± 0.56) mm] of common carotid artery (CCA) in the patients of observation group were all significantly lower than those in patients in the control group ($P$ = 0.000, 0.000, 0.010, respectively). Comparing serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) and creatinine (Cr) levels after treatment with before treatment, there was no significant difference between 2 groups ($P > 0.05$, for all). **Conclusions** Atorvastatin can effectively improve the abnormal blood lipids and soften or even lessen the carotid artery plaques in patients with atherosclerotic cerebral infarction, therefore it is helpful to the second prevention of

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cerebral infarction with no obvious adverse reactions.

【Key words】 Brain infarction; Atherosclerosis; Antilipemic agents

动脉粥样硬化性脑梗死系指颅内动脉出现粥样硬化并形成血栓，使血管管腔狭窄甚至闭塞，导致局灶性急性脑供血不足而发病；临床以肢体乏力或感觉异常为主要表现[1]。治疗以针对病因为主，降低血脂[2]，软化甚至缩小颅内动脉粥样硬化斑块，他汀类调脂药具有降低血清总胆固醇（TC）、甘油三酯（TG）、低密度脂蛋白胆固醇（LDL-C）水平和升高高密度脂蛋白胆固醇（HDL-C）水平，抑制动脉粥样硬化继续恶化之功效。研究发现，他汀类药物除有调脂作用外，还能通过改善血管内皮细胞功能、抑制炎症反应、抑制平滑肌细胞增生和促进凋亡、减少脂质在血管内皮沉积、减少泡沫细胞形成、抑制血小板活性和聚集等，达到稳定斑块作用[3]。为进一步了解阿托伐他汀的调脂疗效和对斑块的作用，我们以动脉粥样硬化性脑梗死患者作为观察对象，分别对其治疗前后血脂水平、颈动脉斑块变化，以及药物安全性进行观察并分析，结果报告如下。

## 对象与方法

一、观察对象

1. 纳入标准 （1）符合1995年第四届全国脑血管病学术会议制订的诊断标准，并经头部CT或MRI检查证实。（2）根据改良TOAST分型符合动脉粥样硬化性血栓形成（AT型）[4]。（3）经超声检查显示双侧颈动脉粥样硬化斑块形成。（4）发病时间 ≤ 24 h。

2. 排除标准 （1）入组前30 d内曾服用其他调脂药。（2）既往有脑卒中或神经精神疾病病史、急性脑出血、恶性肿瘤或风湿免疫性疾病、活动性肝病。（3）血清谷氨酸转氨酶（ALT）水平持续高于正常值上限3倍且原因不明。（4）入组时正在服用环孢素、人类免疫缺陷病毒（HIV）蛋白酶抑制剂（替拉那韦或利托那韦）、丙型肝炎病毒（HCV）蛋白酶抑制剂（特拉匹韦）。

3. 一般资料 根据病例选择标准，选择2013年4月–2014年4月在张家港市第一人民医院神经内科住院治疗的急性动脉粥样硬化性脑梗死患者共92例，男性50例，女性42例；年龄50～74岁，平均（67.52 ± 1.94）岁；病程9～11 h，平均为（10.02 ± 0.41）h；其中合并高血压34例、吸烟史15例、酗酒史7例。采用随机数字表法随机分为阿托伐他汀治疗组（阿托伐他汀组）和对照组，两组患者性别、年龄、病程和既往史等项资料比较，差异无统计学意义（均 $P>0.05$，表1），均衡可比。

二、研究方法

1. 治疗方法 （1）药品：阿托伐他汀钙（规格：20 mg/粒）为美国Pfizer公司产品。（2）给药方法：两组患者入组后分别予以依达拉奉（规格：10 mg，南京先声药业有限公司）30 mg（2次/d）和中成药血栓通（规格：100 mg，广西梧州制药集团有限公司）500 mg（1次/d）静脉滴注，并予拜阿司匹林（规格：100 mg，美国Pfizer公司）100 mg/d口服。阿托伐他汀组患者在此基础上晚餐后1 h顿服20 mg阿托伐他汀钙，治疗3个月；对照组患者除基本治疗措施外，忌食脂质含量较高食物。两组合并高血压或糖尿病患者予以抗高血压、降糖治疗，出院后继续服用拜阿司匹林100 mg/d。（3）注意事项：阿托伐他汀组患者治疗期间禁用其他调脂药物，并严格监测血清ALT、天冬氨酸转氨酶（AST）、肌酸激酶（CK）和肌酐（Cr）水平，以血清ALT水平高于正常值上限3倍为停药标准。

2. 观察指标 （1）实验室检查：所有患者均于入院第2天和治疗第90天时采集空腹肘静脉血5 ml，采用AU5800型全自动生化仪（美国Beckman

**表1** 阿托伐他汀组与对照组患者一般资料的比较

**Table 1.** Comparison of general data between atorvastatin group and control group

| Item | Control (N = 46) | Atorvastatin (N = 46) | $\chi^2$ or $t$ value | $P$ value |
|---|---|---|---|---|
| Sex [case (%)] | | | 0.175 | 0.675 |
| Male | 26 (56.52) | 24 (52.17) | | |
| Female | 20 (43.48) | 22 (47.83) | | |
| Age ($\bar{x} \pm s$, year) | 67.41 ± 2.46 | 67.24 ± 3.17 | 0.287 | 0.775 |
| Duration ($\bar{x} \pm s$, h) | 9.92 ± 0.43 | 10.12 ± 0.58 | -1.879 | 0.060 |
| Hypertension [case (%)] | 16 (34.78) | 18 (39.13) | 0.187 | 0.666 |
| Smoking [case (%)] | 8 (17.39) | 7 (15.22) | 0.080 | 0.778 |
| Alcoholism [case (%)] | 3 ( 6.52) | 4 ( 8.70) | 0.155 | 0.694 |

$t$ test for comparison of age and duration, and $\chi^2$ test for comparison of others

**表2** 阿托伐他汀组与对照组患者治疗前后血脂水平的比较($\bar{x} \pm s$,mmol/L)

**Table 2.** Comparison of serum lipid levels between 2 groups before and after treatment ($\bar{x} \pm s$, mmol/L)

| Group | N | TC | | TG | | LDL-C | | HDL-C | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Control | 46 | 6.51±0.82 | 5.24±0.68 | 3.72±0.84 | 3.33±0.47 | 5.43±0.88 | 4.78±0.86 | 0.79±0.26 | 0.85±0.32 |
| Atorvastatin | 46 | 6.47±1.13 | 4.23±0.92 | 3.62±0.72 | 2.46±0.28 | 5.23±0.93 | 2.52±0.38 | 0.81±0.34 | 1.13±0.41 |

TC, total cholesterol, 总胆固醇; TG, triglyceride, 甘油三酯; LDL-C, low-density lipoprotein cholesterol, 低密度脂蛋白胆固醇; HDL-C, high-density lipoprotein cholesterol, 高密度脂蛋白胆固醇。The same for Table 3

**表3** 阿托伐他汀组与对照组患者治疗前后血脂水平的重复测量设计的方差分析表

**Table 3.** ANOVA for repeated measurement design of blood lipid levels between 2 groups before and after treatment

| Source of variation | *SS* | df | *MS* | *F* value | *P* value | Source of variation | *SS* | df | *MS* | *F* value | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TC | | | | | | LDL-C | | | | | |
| Treatment | 41.338 | 1 | 41.338 | 70.079 | 0.000 | Treatment | 10.741 | 1 | 10.741 | 20.011 | 0.000 |
| Time | 56.912 | 1 | 56.912 | 96.480 | 0.000 | Time | 92.570 | 1 | 92.570 | 172.458 | 0.000 |
| Treatment×time | 63.964 | 1 | 63.964 | 108.434 | 0.000 | Treatment×time | 8.390 | 1 | 8.390 | 15.631 | 0.000 |
| Error between groups | 6792.867 | 184 | 36.918 | | | Error between groups | 2009.412 | 184 | 10.921 | | |
| Error within group | 106.179 | 184 | 0.590 | | | Error within group | 96.619 | 180 | 0.537 | | |
| TG | | | | | | HDL-C | | | | | |
| Treatment | 9.311 | 1 | 9.311 | 23.813 | 0.000 | Treatment | 2.270 | 1 | 2.270 | 9.284 | 0.003 |
| Time | 22.692 | 1 | 22.692 | 57.911 | 0.000 | Time | 8.860 | 1 | 8.860 | 36.230 | 0.000 |
| Treatment×time | 18.746 | 1 | 18.746 | 47.840 | 0.000 | Treatment×time | 1.305 | 1 | 1.305 | 4.279 | 0.021 |
| Error between groups | 2101.624 | 184 | 11.422 | | | Error between groups | 413.373 | 184 | 2.247 | | |
| Error within group | 70.533 | 180 | 0.392 | | | Error within group | 44.019 | 180 | 0.305 | | |

Coulter有限公司)检测血清TC、TG、LDL-C和HDL-C水平,以及血清ALT、AST、CK和Cr水平。(2)颈动脉超声检查:患者分别于入院第2天和治疗第90天时,以HDI5000型彩色多普勒超声诊断仪(荷兰Philips公司)行颈动脉超声检测,扫描频率12 MHz,于局部颈总动脉结构显示最清晰部位连续测量3次动脉管壁内-中膜厚度(IMT),取平均值。以阶段性IMT ≥ 1.00 mm为增厚、IMT ≥ 1.50 mm且突入管腔或局限性IMT > 周围50%为斑块形成;测量斑块横截面最大面积和厚度[5],以斑块横截面最大面积缩小、斑块厚度变薄或IMT变小为好转。

3. 统计分析方法 采用SPSS 13.0统计软件进行数据计算与分析。计数资料以相对数构成比(%)或率(%)表示,行$\chi^2$检验;计量资料以均数±标准差($\bar{x} \pm s$)表示,采用重复测量设计的方差分析。以$P \leq 0.05$为差异具有统计学意义。

## 结 果

一、实验室指标评价

1. 治疗前后血脂变化 两组患者治疗前血清TC、TG、LDL-C和HDL-C水平比较,差异无统计学意义(均$P > 0.05$),治疗后血清TC、TG和LDL-C水平下降(均$P < 0.05$)、HDL-C水平升高($P < 0.05$);阿托伐他汀组各项实验室指标改善程度均优于对照组且差异具有统计学意义($P < 0.05$;表2,3)。

2. 治疗前后心脏功能、肝肾功能变化 两组患者治疗期间均未出现肌肉酸痛等药物不良反应,监测血清ALT、AST、CK和Cr表达水平均于正常值范围,两组治疗前后差异未达到统计学意义(均$P > 0.05$;表4,5)。

二、颈动脉超声评价

两组患者治疗前斑块面积、厚度和IMT差异无统计学意义(均$P > 0.05$);治疗后阿托伐他汀组斑块面积缩小、斑块厚度变薄、IMT变小,与治疗前和对照组比较,差异有统计学意义(均$P < 0.05$;表6,7)。

## 讨 论

我国动脉粥样硬化性脑梗死占缺血性卒中亚型分型的首位,其发病原因与多种因素有关,颈动脉粥样硬化为常见原因之一[6]。内-中膜增厚是颈

**表4** 阿托伐他汀组与对照组患者治疗前后各项实验室指标的比较($\bar{x} \pm s$)

**Table 4.** Comparison of laboratory indexes between 2 groups before and after treatment ($\bar{x} \pm s$)

| Group | N | ALT (U/L) | | AST (U/L) | | CK (U/L) | | Cr (μmol/L) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Control | 46 | 22.71±7.33 | 23.53±5.65 | 18.92±9.34 | 18.32± 9.47 | 84.37±12.34 | 85.23±17.43 | 73.67±9.45 | 74.31±8.73 |
| Atorvastatin | 46 | 21.83±4.84 | 22.67±4.98 | 19.21±8.39 | 18.76±10.23 | 83.84±11.23 | 84.65±12.65 | 74.12±8.34 | 75.02±7.94 |

ALT, alanine aminotransferase, 丙氨酸转氨酶; AST, aspartate aminotransferase, 天冬氨酸转氨酶; CK, creatine kinase, 肌酸激酶; Cr, creatinine, 肌酐 。The same for Table 5

**表5** 阿托伐他汀组与对照组患者治疗前后各项实验室指标的重复测量设计的方差分析表

**Table 5.** ANOVA for repeated measurement design of laboratory indexes between 2 groups before and after treatment

| Source of variation | *SS* | df | *MS* | *F* value | *P* value | Source of variation | *SS* | df | *MS* | *F* value | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ALT | | | | | | CK | | | | | |
| Treatment | 45.099 | 1 | 45.099 | 1.883 | 0.172 | Treatment | 131.303 | 1 | 131.303 | 0.711 | 0.400 |
| Time | 30.852 | 1 | 30.852 | 1.288 | 0.258 | Time | 47.519 | 1 | 47.519 | 0.257 | 0.613 |
| Treatment×time | 28.689 | 1 | 28.689 | 1.198 | 0.275 | Treatment×time | 234.273 | 1 | 234.273 | 1.269 | 0.262 |
| Error between groups | 99 766.986 | 184 | 518.788 | | | Error between groups | 1 312 990.123 | 184 | 7135.816 | | |
| Error within group | 4 310.067 | 180 | 23.945 | | | Error within group | 33 240.025 | 180 | 184.667 | | |
| AST | | | | | | Cr | | | | | |
| Treatment | 273.529 | 1 | 273.529 | 2.827 | 0.094 | Treatment | 9.884 | 1 | 9.884 | 0.139 | 0.710 |
| Time | 44.205 | 1 | 44.205 | 0.457 | 0.500 | Time | 82.798 | 1 | 82.798 | 1.164 | 0.282 |
| Treatment×time | 28.283 | 1 | 28.283 | 0.292 | 0.589 | Treatment×time | 15.834 | 1 | 15.834 | 0.223 | 0.638 |
| Error between groups | 89 070.656 | 184 | 389.422 | | | Error between groups | 1 048 625.557 | 184 | 5629.490 | | |
| Error within group | 17 417.049 | 180 | 96.761 | | | Error within group | 12 799.367 | 180 | 71.108 | | |

动脉粥样硬化的早期征象，表现为内膜粗糙增厚并逐渐形成斑块，斑块厚度达到一定程度即引起颈动脉狭窄和狭窄远端脑血流低灌注状态；斑块脱落则形成微栓子导致颅内动脉栓塞。脂质代谢紊乱是颈动脉粥样硬化的关键因素，血清TC、TG、LDL-C任一项升高、HDL-C降低均可导致动脉粥样硬化[7]。据文献报道，他汀类调脂药可使缺血性卒中相对危险度降低22%，因此无冠心病病史的高脂血症患者血清LDL-C水平应降低50%或降至1.80 mmol/L，此亦为预防脑卒中复发的重要措施之一[8]。

本研究结果显示，治疗3个月后，阿托伐他汀组患者血清TC、TG和LDL-C水平降低、HDL-C水平升高，与未接受调脂药治疗的急性脑梗死患者相比，血脂水平显著改善，提示阿托伐他汀具有良好的调脂作用，与文献报道的结果相一致[9]。阿托伐他汀的作用机制是使肝细胞合成胆固醇减少，反馈性上调细胞表面LDL-C受体表达使细胞LDL受体数目增加、活性增强，从而加速循环中LDL和极低密度脂蛋白(VLDL)残粒的清除；与此同时，尚可抑制肝细胞合成VLDL，在降低血清TC和LDL-C水平的同时降低TG水平并升高HDL-C水平。阿托伐他汀作为一种3-羟基-3-甲基戊二酰辅酶A(HMG-CoA)还原酶抑制剂，该药物是目前应用于临床最广泛的一种他汀类药物，并且为他汀类药物中调脂力度很强的一种药物，是抗高胆固醇血症的首选药物，本研究阿托伐他汀组患者经阿托伐他汀治疗3个月后斑块缩小、斑块厚度变薄，IMT变小，提示阿托伐他汀具有较好的抗动脉粥样硬化斑块效果。阿托伐他汀的调脂作用主要通过以下途径实现：抑制脂质在颈动脉斑块内的聚集，使斑块形成速度减慢并促进斑块的分解；减少C-反应蛋白(CRP)、白细胞介素-6(IL-6)等炎性因子的产生，减轻炎症反应而抑制斑块形成；有效抑制血管平滑肌细胞增生从而减少斑块组成成分、缩小斑块体积[10-11]；通过多种途径使内皮一氧化氮合酶(eNOS)表达上调，增加一氧化氮的生物合成和生物利用度、防止自由基级联反应的启动而延缓或逆转颈动脉粥样硬化，以增强斑块稳定性使内-中膜变薄[12]。本研究阿托伐他汀组患者治疗期间无一例发生肌肉疼痛等药物不良反应，以及ACT、AST、CK和Cr等实验室指标异常现象。

**表6** 阿托伐他汀与对照组患者治疗前后颈动脉斑块的比较($\bar{x} \pm s$)

**Table 6.** Comparison of carotid plaques between 2 groups before and after treatment ($\bar{x} \pm s$)

| Item | N | Before treatment | After treatment |
|---|---|---|---|
| Plaque size ($mm^2$) | | | |
| Control | 46 | 26.78 ± 12.38 | 24.42 ± 10.33 |
| Atorvastatin | 46 | 25.80 ± 11.72 | 20.25 ± 0.32 |
| Plaque thickness (mm) | | | |
| Control | 46 | 2.94 ± 0.23 | 1.93 ± 0.23 |
| Atorvastatin | 46 | 2.89 ± 0.17 | 0.59 ± 0.13 |
| IMT (mm) | | | |
| Control | 46 | 1.83 ± 0.48 | 1.63 ± 0.56 |
| Atorvastatin | 46 | 1.78 ± 0.74 | 1.32 ± 0.67 |

IMT, intima-media thickness, 内-中膜厚度。The same for Table 7

**表7** 阿托伐他汀组与对照组患者颈动脉斑块重复测量设计的方差分析表

**Table 7.** ANOVA for repeated measurement design of carotid atherosclerotic plaques between 2 groups

| Source of variation | *SS* | df | *MS* | *F* value | *P* value |
|---|---|---|---|---|---|
| Plaque size | | | | | |
| Treatment | 4.115 | 1 | 4.115 | 27.804 | 0.000 |
| Time | 9.482 | 1 | 9.482 | 64.109 | 0.000 |
| Treatment × time | 1.392 | 1 | 1.392 | 9.413 | 0.002 |
| Error between groups | 467.708 | 184 | 2.542 | | |
| Error within group | 26.622 | 180 | 0.148 | | |
| Plaque thickness | | | | | |
| Treatment | 0.031 | 1 | 0.031 | 67.020 | 0.000 |
| Time | 0.052 | 1 | 0.052 | 7.429 | 0.006 |
| Treatment × time | 0.004 | 1 | 0.004 | 9.395 | 0.003 |
| Error between groups | 1.233 | 184 | 0.007 | | |
| Error within group | 0.083 | 180 | 0.000 | | |
| IMT | | | | | |
| Treatment | 1.532 | 1 | 1.532 | 6.383 | 0.010 |
| Time | 1.610 | 1 | 1.610 | 6.708 | 0.009 |
| Treatment × time | 1.251 | 1 | 1.251 | 5.213 | 0.012 |
| Error between groups | 1.521 | 184 | 0.008 | | |
| Error within group | 43.182 | 180 | 0.240 | | |

综上所述，阿托伐他汀可有效降低动脉粥样硬化性脑梗死患者血清TC、TG和LDL-C水平，升高HDL-C水平，对颈动脉斑块具有一定的抑制作用且安全性良好。

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