

doi: 10.13241/j.cnki.pmb.2017.31.025

阿托伐他汀联合双抗血小板治疗对脑梗死患者疗效及对血清炎性因子水平的影响

邓立军 张淑琴 魏进 吴丹 丁亿

(江汉大学附属医院神经内科 湖北 武汉 430015)

摘要 目的:观察阿托伐他汀联合双抗血小板治疗对脑梗死患者脑血管事件复发率、神经功能缺损、血清炎性因子水平的影响,探讨其疗效和安全性。**方法:**选择2014年6月到2016年6月我院收治的脑梗死患者110例,按照随机数字表分为实验组和对照组,每组55例。两组患者均接受脑梗死常规治疗,对照组服用阿托伐他汀和阿司匹林,实验组服用阿托伐他汀、阿司匹林和氯吡格雷。在治疗前和治疗后2周、4周分别采用美国国立卫生研究院卒中量表(NIHSS)对患者神经功能缺损程度进行评分,检测血清炎性因子白细胞介素-6(IL-6)、白细胞介素-8(IL-8)和肿瘤坏死因子- α (TNF- α)水平,随访4周并统计脑血管事件复发率。**结果:**两组患者治疗2周、4周后NIHSS评分均低于治疗前($P<0.05$),且实验组低于对照组($P<0.05$)。两组患者治疗2周、4周后血清IL-6、IL-8和TNF- α 均低于治疗前($P<0.05$),治疗4周后,实验组血清IL-6、IL-8和TNF- α 水平均明显低于对照组($P<0.05$)。实验组患者脑血管事件复发率低于对照组,但差异无统计学意义($P>0.05$)。**结论:**阿托伐他汀联合双抗血小板疗法具备一定的抗炎作用,有助于脑梗死患者神经功能缺损恢复,且脑血管事件复发率低,值得临床应用。

关键词:阿托伐他汀;双抗血小板疗法;脑梗死;神经功能缺损;血清炎性因子

中图分类号:R743 **文献标识码:**A **文章编号:**1673-6273(2017)31-6107-04

Effect of Atorvastatin combined with Double Antiplatelet Therapy on Patients with Cerebral Infarction

DENG Li-jun, ZHANG Shu-qin, WEI Jin, WU Dan, DING Yi

(Department of Neurology, Affiliated Hospital of Jiangnan University, Wuhan, Hubei, 430015, China)

ABSTRACT Objective: To observe the effect of Atorvastatin combined with double antiplatelet therapy on the recurrence rate of cerebral vascular events, neurological impairment and serum inflammatory factor level in patients with cerebral infarction, and to explore its efficacy and safety. **Methods:** A total of 110 patients with cerebral infarction, who were treated in Affiliated Hospital of Jiangnan University from June 2014 to June 2016, were selected and randomly divided into experimental group($n=55$) and control group($n=55$). The two groups received routine treatment of cerebral infarction; the control group received Atorvastatin and Aspirin, and the experimental group received Atorvastatin, Aspirin and Clopidogrel. Before treatment, 2 weeks and 4 weeks after treatment, the neurological impairment of patients was evaluated by national institutes of health stroke scale (NIHSS) scores. The levels of serum inflammatory factors such as interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor- α (TNF- α) were detected. All the patients were followed up for 4 weeks, and the recurrence rate of cerebral vascular events was recorded. **Results:** The NIHSS scores of two groups 2 weeks and 4 weeks after treatment were lower than those before treatment ($P<0.05$), and the NIHSS scores of experimental group was lower than that of the control group ($P<0.05$). The levels of serum IL-6, IL-8 and TNF- α in the two groups 2 weeks and 4 weeks after treatment were lower than those before the treatment ($P<0.05$). The levels of serum IL-6, IL-8 and TNF- α in the experimental group were lower than those in the control group 4 weeks after treatment ($P<0.05$). The recurrence rate of cerebral vascular events in the experimental group was lower than that in the control group, but the difference was not statistically significant ($P>0.05$). **Conclusion:** Combination of Atorvastatin and double antiplatelet therapy has certain anti-inflammatory effects, and it is helpful to the recovery of neurological impairment in patients with cerebral infarction. The recurrence rate of cerebral vascular events is low, so it is worthy of clinical application.

Key words: Atorvastatin; Double antiplatelet therapy; Cerebral infarction; Neurological impairment; Serum inflammatory factor

Chinese Library Classification(CLC): R743 **Document code:** A

Article ID: 1673-6273(2017)31-6107-04

前言

作者简介:邓立军(1981-),男,本科,主治医师,研究方向:脑血管病、癫痫及神经变性疾病,E-mail: yxw5623@126.com

(收稿日期:2017-07-05 接受日期:2017-07-28)

脑梗死又称缺血性卒中,是指由于各种原因导致的脑局部血液供应障碍,脑组织缺血缺氧,进展成局限性脑组织缺血性坏死或脑软化^[1,2]。随着我国人口老龄化进程加快,其发病率在部分地区有逐渐上升趋势,已经成为我国最重要的致残病因^[3]。阿司匹林类药物是脑梗死治疗的常用药物,而他汀类药物降脂

治疗可以预防动脉粥样硬化,稳定斑块,对脑缺血性损伤有一定的保护作用^[4,5]。目前两类药物在脑梗死治疗中均有应用,但是关于阿托伐他汀联合双抗血小板治疗脑梗死对患者神经功能缺损方面的报道较少^[6]。因此,本研究采用阿托伐他汀联合双抗血小板治疗脑梗死合并颈动脉粥样硬化患者,发现能够有效促进患者神经功能缺损恢复,旨在为临床治疗提供参考。现报道如下:

1 资料和方法

1.1 一般资料

选择2014年6月到2016年6月我院收治的脑梗死患者110例。纳入标准:(1)符合全国第四届脑血管病学术会议修订的诊断标准^[7],且合并颈动脉粥样硬化者;(2)首次发病者且发病时间到入院时间在72小时内;(3)患者意识清楚,自愿参加研究并签署知情同意书。排除标准:(1)依从性差者或有其他可能影响美国国立卫生研究院卒中量表(NIHSS)评分的神经系统疾病者^[8];(2)对研究所涉及药物过敏者或不能使用研究涉及药物者;(3)合并严重心、肺、肝、肾功能不全者;(4)入院前2个月内进行过抗凝或溶栓治疗者。所有患者按照随机数字表分为对照组和实验组,每组55例。对照组,男性30例,女性25例,年龄48-72岁,平均年龄(62.5±6.1)岁,平均病程(15.8±7.1)h,治疗前NIHSS评分为(11.5±5.7)分;实验组,男性28例,女性27例,年龄49-73岁,平均年龄(63.1±5.9)岁,平均病程(15.6±7.3)h,治疗前NIHSS评分为(11.9±6.1)分。两组患者的性别、年龄、治疗前NIHSS评分等一般情况比较无统计学差异($P>0.05$),具有可比性。本研究经医院伦理委员会审核通过。

1.2 实验方法

1.2.1 治疗方法 两组患者均给予阿托伐他汀(生产厂家:北京嘉林药业股份有限公司,国药准字:H20093819,规格:20mg)20mg/d,阿司匹林肠溶片(生产厂家:甘肃祁连山药业股份

有限公司,国药准字:H62021159,规格:25mg)100mg/d,依达拉奉注射液(生产厂家:扬子江药业集团南京海陵药业有限公司,国药准字:H20130133,规格:5mL:10mg),并根据患者个体情况给予降压、降糖等其他药物,患者均接受低胆固醇饮食。实验组患者加用氯吡格雷片(生产厂家:乐普药业股份有限公司,国药准字:H20123116,规格:75mg)75mg/d。两组患者均住院两周,出院后对照组继续口服阿托伐他汀20mg/d加阿司匹林肠溶片100mg/d 4周。实验组口服阿托伐他汀20mg/d,阿司匹林肠溶片100mg/d和氯吡格雷片75mg/d 2周,之后改为阿托伐他汀20mg/d加阿司匹林肠溶片100mg/d 2周。

1.2.2 检测指标及方法 (1)神经功能缺损程度评分:采用NIHSS评分,于治疗前,治疗2周,4周各评定一次。评分越低,表示神经功能缺损恢复效果越好。

(2)血清炎症因子水平:于治疗前,治疗2周,治疗4周时清晨空腹抽取静脉血,离心分离血清后,通过酶联免疫吸附法检测白介素-6(IL-6)、白介素-8(IL-8)和肿瘤坏死因子- α (TNF- α)水平,操作均按照试剂盒说明书进行。

(3)脑血管事件复发率:自出院后通过电话和门诊随访4周,统计治疗后两组患者脑血管事件复发率。

1.3 统计学方法

采用SPSS19.0统计软件进行统计分析,计量数据用($\bar{x} \pm s$)表示,组间比较采用t检验;计数资料以百分比表示,组间比较采用 χ^2 检验, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者 NIHSS 评分比较

治疗前,两组患者NIHSS评分比较差异无统计学意义($P>0.05$),两组患者治疗2周、4周后NIHSS评分均低于治疗前($P<0.05$),且实验组低于对照组,差异具有统计学意义($P<0.05$),见表1。

表1 两组患者治疗前后 NIHSS 评分比较

Table 1 Comparison of NIHSS scores between two groups before and after treatment

Groups	n	NIHSS scores		
		Before treatment	2 weeks after treatment	4 weeks after treatment
Control group	55	11.5±5.7	5.9±2.7*	4.2±2.9*
Experimental group	55	11.9±6.1	4.8±2.5*	3.1±2.3*
t		0.355	2.217	2.204
P		0.723	0.029	0.030

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

2.2 两组患者治疗前后血清炎症因子水平比较

两组患者治疗2周、4周后血清IL-6、IL-8和TNF- α 水平均明显低于治疗前($P<0.05$),治疗4周后,实验组血清IL-6、IL-8和TNF- α 水平均明显低于对照组,差异具有统计学意义($P<0.05$),见表2。

2.3 两组患者脑血管事件复发率比较

实验组患者脑血管事件复发率低于对照组,但经过连续性校正差异无统计学意义($P>0.05$),见表3。

3 讨论

脑梗死是中老年人常见病和多发病,脑部血液供应障碍会导致患者的脑部组织和神经受到损伤,临床表现为偏瘫、语言障碍等。如果不能及时有效对患者进行治疗,就会有较高的死亡率、致残率和复发率^[9-11]。据文献报道,脑梗死后1年内复发率为11.1%,5年累积复发率高达26.4%,给患者和家庭带来了沉重的负担^[12]。如何有效降低脑梗死后的致残率和复发率,是

表 2 两组患者治疗前后血清炎症因子水平比较

Table 2 Comparison of serum inflammatory factors levels between two groups before and after treatment

Groups	n	Time	IL-6(pg/mL)	IL-8(ng/mL)	TNF- α (ng/L)
Control group	55	Before treatment	18.7 $\pm$ 5.7	2.6 $\pm$ 1.2	36.1 $\pm$ 8.9
		2 weeks after treatment	7.9 $\pm$ 2.4*	1.7 $\pm$ 0.8*	27.3 $\pm$ 7.6*
		4 weeks after treatment	7.2 $\pm$ 2.2*	0.9 $\pm$ 0.3*	23.2 $\pm$ 7.1*
Experimental group	55	Before treatment	18.3 $\pm$ 5.6	2.7 $\pm$ 1.1	36.7 $\pm$ 9.1
		2 weeks after treatment	6.7 $\pm$ 2.3*	1.5 $\pm$ 0.7*	23.2 $\pm$ 8.0*
		4 weeks after treatment	6.3 $\pm$ 1.9* [#]	0.5 $\pm$ 0.2* [#]	19.2 $\pm$ 6.6* [#]

Note: Compared with before treatment, *P<0.05; Compared with control group, [#]P<0.05.

表 3 两组患者脑血管事件复发率比较

Table 3 Comparison of recurrence rates of cerebral vascular events between two groups

Groups	n	Cases of cerebral vascular events(n)	Recurrence rates(%)
Control group	55	3	5.45
Experimental group	55	0	0*

Note: Compared with control group, *P>0.05.

当前研究的热点。随着对脑梗死病理基础研究的深入,其病理基础主要包括血管壁病变、血液成分和血液动力学改变,动脉粥样硬化是疾病发生发展的主要基础,颈动脉粥样硬化作为脑梗死的独立危险因素已经获得众多临床研究支持。本研究中采用阿托伐他汀进行降脂、稳定动脉斑块。阿托伐他汀可以通过抑制肝脏合成途径中的胆固醇限速酶和还原酶的活性,阻断或减少肝内胆固醇的合成;同时刺激肝脏 LDL-C 受体合成增加,起到降低血清中 LDL-C 和胆固醇的作用^[13-15]。另有研究表明他汀类药物可以降低血清炎症因子水平,减轻脑梗死患者急性期的炎症反应^[16,17]。此外,有研究显示他汀类药物可能通过抗兴奋毒性神经损害,降低脑梗死后血浆 NO 水平和抗氧化作用等途径起到神经保护作用^[18]。

本研究中阿托伐他汀能有效降低血清 IL-6、IL-8 和 TNF- α 的水平,提示阿托伐他汀减轻炎症反应可能是通过降低血清 IL-6 水平,从而降低基质金属蛋白酶-1(MMP-1)水平,保护血脑屏障^[7];降低血清 IL-8 水平,可以减少中性粒细胞趋化和组织细胞损伤^[8];降低血清 TNF- α 水平,可以保护血管内皮细胞三个方面起作用。研究中使用的阿司匹林能够通过抑制环氧合酶和血栓素 A2 的分泌,抑制血小板活化聚集功能^[19-21];氯吡格雷能够通过抑制血小板膜二磷酸腺苷受体抑制血小板活化聚集,两者联合应用可以增强抗血小板聚集作用^[22]。临床氯吡格雷疗效优于阿司匹林,然而近年来研究表明,阿司匹林和氯吡格雷都存在药物抵抗现象^[23,24]。但是两者联用时,并不会抑制胶原诱导的血小板聚集,两者联用具有协同作用^[25-27]。需要注意的是,长期应用双联抗血小板治疗可能导致出血性事件风险增加^[28]。在短程治疗研究中,双联抗血小板治疗的安全性良好,有研究证实对短暂性脑缺血发作(TIA)患者采用阿司匹林联合氯吡格雷治疗 21 d,能够安全有效降低脑卒中 3 个月内复发的风险,和本研究的结果一致^[29,30]。本研究实验组脑血管事件复发率低于对照组,但是由于病例数较少,进行连续性校正后差异无统计学意义,本治疗方案是否能有效降低脑梗死患者的复发率还有待于进一步的大样本研究证实。

综上所述,阿托伐他汀联合双抗血小板能有效促进患者神经功能缺损恢复,降低血清炎症因子水平,且脑血管事件复发率低,值得临床推广应用。

参考文献(References)

- [1] Bongiorno GT, Hockmuller MCJ, Klein C, et al. Decompressive craniotomy for the treatment of malignant infarction of the middle cerebral artery:mortality and outcome [J]. Arq Neuropsiquiatr, 2017, 75 (7): 424-428
- [2] Shao L, Wang M, Ge XH, et al. The use of susceptibility-weighted imaging to detect cerebral microbleeds after lacunar infarction[J]. Eur Rev Med Pharmacol Sci, 2017, 21(13): 3105-3112
- [3] Lo WL, Mao YR, Li L, et al. Prospective clinical study of rehabilitation interventions with multisensory interactive training in patients with cerebral infarction: study protocol for a randomised controlled trial[J]. Trials, 2017, 18(1): 173
- [4] 郭爱红,王丙聚,韩晓芳.阿司匹林联合氯吡格雷治疗急性脑梗死并脑微出血的临床疗效 [J]. 实用心脑血管病杂志, 2017, 25(5): 109-111
- Guo Ai-hong, Wang Bing-ju, Han Xiao-fang, et al. Clinical Effect of Aspirin Combined with Clopidogrel in Treating Acute Cerebral Infarction Patients Complicated with Cerebral Microbleeds[J]. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease, 2017, 25 (5): 109-111
- [5] 佟旭,周全,史楠,等.阿托伐他汀治疗大动脉粥样硬化狭窄性脑梗死的有效性分析[J].中国全科医学, 2015, 20(32): 3977-3980
- Tong Xu, Zhou Quan, Shi Nan, et al. Efficacy of Atorvastatin in the Treatment of Arteriosclerosis-induced Cerebral Infarction[J]. Chinese General Medicine, 2015, 20(32): 3977-3980
- [6] Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack[J]. N Engl J Med, 2016, 375(1): 35-43
- [7] 刘光均. 早期综合康复治疗对急性脑梗死疗效分析 [J]. 医药前沿, 2017, 7(14): 187-188

- Liu Guang-jun. Curative effect analysis of early comprehensive rehabilitation therapy on acute cerebral infarction [J]. *Frontiers of Medicine*, 2017, 7(14): 187-188
- [8] 潘成德,唐明山,邹耀兵,等.阿替普酶静脉溶栓治疗急性缺血性脑卒中疗效观察[J].海南医学, 2017, 27(8): 1245-1247
- Pan Cheng-de, Tang Ming-shan, Zou Yao-bing, et al. Clinical effect of alteplase intravenous thrombolysis in the treatment of acute ischemic stroke[J]. *Hainan Medical Journal*, 2017, 27(8): 1245-1247
- [9] Mack MJ, Acker MA, Gelijns AC, et al. Effect of Cerebral Embolic Protection Devices on CNS Infarction in Surgical Aortic Valve Replacement: A Randomized Clinical Trial [J]. *JAMA*, 2017, 318(6): 536-547
- [10] Wang T, Gong Y, Shi Y, et al. Feasibility of dual-low scheme combined with iterative reconstruction technique in acute cerebral infarction volume CT whole brain perfusion imaging [J]. *Exp Ther Med*, 2017, 14(1): 163-168
- [11] Sato K, Shimizu H, Inoue T, et al. Temporal and Spatial Changes in Cerebral Blood Flow during Management for Preventing Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: Serial Semiquantitative Analysis [J]. *J Stroke Cerebrovasc Dis*, 2017, 26(9): 2027-2037
- [12] Lehtola H, Airaksinen KEJ, Hartikainen P, et al. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk[J]. *Eur J Neurol*, 2017, 24(5): 719-725
- [13] 董丰,杨承健,叶新和,等.阿托伐他汀对心肌梗死患者的保护作用及其机制研究[J].现代生物医学进展, 2016, 16(31): 6076-6079
- Dong Feng, Yang Cheng-jian, Ye Xin-he, et al. Study of the Protective Effect and Mechanisms of Atorvastatin in Patients with Acute Myocardial Infarction [J]. *Progress in Modern Biomedicine*, 2016, 16(31): 6076-6079
- [14] 王京坡,岳龙,张静,等.不同剂量阿托伐他汀对 PCI 术后急性心肌梗死患者血脂、hs-CRP 及心功能的影响[J].现代中西医结合杂志, 2017, 26(19): 2141-2143
- Wang Jing-po, Yue long, Zhang Jing, et al. Effects of different doses of atorvastatin on blood lipids, hs-CRP and cardiac function in patients with acute myocardial infarction after PCI [J]. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, 2017, 26(19): 2141-2143
- [15] Deguchi I, Horiuchi Y, Hayashi T, et al. Effects of rosuvastatin on serum lipids and arteriosclerosis in dyslipidemic patients with cerebral infarction[J]. *J Stroke Cerebrovasc Dis*, 2014, 23(8): 2007-2011
- [16] Walker ME, Souza PR, Colas RA, et al. 13-Series resolvins mediate the leukocyte-platelet actions of atorvastatin and pravastatin in inflammatory arthritis[J]. *FASEB J*, 2017, 31(8): 3636-3648
- [17] Shen J, Huang KY, Zhu Y, et al. Effect of statin treatment on vasospasm-related morbidity and functional outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis[J]. *J Neurosurg*, 2017, 127(2): 291-301
- [18] 司友锋.阿托伐他汀对急性脑梗死患者神经功能、血清 NO 水平及脑血管储备的影响[J].山东医药, 2015, 57(32): 44-45
- Si You-feng. Effect of atorvastatin on neurological function, serum NO level and cerebrovascular reserve in patients with acute cerebral infarction[J]. *Shandong Medical Journal*, 2015, 57(32): 44-45
- [19] 麻伟兴,王保平,张翼,等.血栓通注射液与阿司匹林对急性复发性脑梗死的临床研究[J].中国临床药理学杂志, 2017, 33(6): 554-557
- Ma Wei-xing, Wang Bao-ping, Zhang Yi, et al. Clinical trial of Xueshuantong injection combined with aspirin in patients with recurrent acute cerebral infarction [J]. *Chinese Journal of Clinical Pharmacology*, 2017, 33(6): 554-557
- [20] 张建强,高红安,宋程光,等.普罗布考联合阿司匹林溶解治疗颈动脉斑块脑梗死的临床效果观察[J].现代生物医学进展, 2017, 17(5): 919-922
- Zhang Jian-qiang, Gao Hong-an, Song Cheng-guang, et al. Clinical effect observation of probucol combined with aspirin dissolution in the treatment of carotid atherosclerotic plaques and cerebral infarction [J]. *Progress in Modern Biomedicine*, 2017, 17(5): 919-922
- [21] Backman JD, Yerges-Armstrong LM, Horenstein RB, et al. Prospective Evaluation of Genetic Variation in Platelet Endothelial Aggregation Receptor 1 Reveals Aspirin-Dependent Effects on Platelet Aggregation Pathways[J]. *Clin Transl Sci*, 2017, 10(2): 102-109
- [22] Koziol K, Van der Merwe V, Yakiwchuk E, et al. Dual antiplatelet therapy for secondary stroke prevention: Use of clopidogrel and acetylsalicylic acid after noncardioembolic ischemic stroke [J]. *Can Fam Physician*, 2016, 62(8): 640-645
- [23] Lu M. Report: Impact of drug combination of clopidogrel and pantoprazole In the prognosis of patients with transient ischemic attack[J]. *Pak J Pharm Sci*, 2017, 30(1): 217-221
- [24] 林慈宽. 氯吡格雷对缺血性脑血管病患者阿司匹林抵抗影响的临床研究[J].陕西医学杂志, 2016, 45(9): 1136-1138
- Lin Ci-kuan. Clinical study of clopidogrel on aspirin resistance in patients with ischemic cerebrovascular disease [J]. *Shaanxi Medical Journal*, 2016, 45(9): 1136-1138
- [25] Michiels JJ, Berneman Z, Gadisseur A, et al. Aspirin-responsive, migraine-like transient cerebral and ocular ischemic attacks and erythromelalgia in JAK2-positive essential thrombocythemia and polycythemia vera[J]. *Acta Haematol*, 2015, 133(1): 56-63
- [26] Ohnuki Y, Ohnuki Y, Kohara S, et al. Dual Therapy with Aspirin and Cilostazol May Improve Platelet Aggregation in Noncardioembolic Stroke Patients: A Pilot Study[J]. *Intern Med*, 2017, 56(11): 1307-1313
- [27] Zi-Liang W, Xiao-Dong L, Tian-Xiao L, et al. Intravenous administration of tirofiban versus loading dose of oral clopidogrel for preventing thromboembolism in stent-assisted coiling of intracranial aneurysms [J]. *Int J Stroke*, 2017, 12(5): 553-559
- [28] 张秋瓚,王艳荣,王秀茹,等.双联抗血小板治疗相关上消化道出血的临床特征[J].中国老年学杂志, 2017, 37(12): 2968-2969
- Zhang Qiu-zan, Wang Yan-rong, Wang Xiu-ru, et al. Clinical features of double antiplatelet therapy in patients with upper gastrointestinal bleeding[J]. *Chinese Journal of Gerontology*, 2017, 37(12): 2968-2969
- [29] Lehman LL, Beate J, Kapur K, et al. Workup for Perinatal Stroke Does Not Predict Recurrence[J]. *Stroke*, 2017, 48(8): 2078-2083
- [30] Zhang YB, Yin Z, Han X, et al. Association of circulating high-sensitivity C-reactive protein with late recurrence after ischemic stroke[J]. *Neuroreport*, 2017, 28(10): 598-603