

doi: 10.13241/j.cnki.pmb.2017.07.025

血栓通联合依达拉奉对老年急性脑梗死患者氧化低密度脂蛋白和 MMPs 水平的影响及临床疗效 *

任 蓓¹ 张爱香¹ 杨云鹏¹ 李 娟¹ 王 静²

(1 西安市第四医院 神经内科 陕西 西安 710004; 2 西安交通大学第二附属医院 神经内科 陕西 西安 710004)

摘要 目的:探讨血栓通联合依达拉奉对老年急性脑梗死患者氧化低密度脂蛋白及 MMPs 水平的影响及临床疗效。**方法:**收集我院收治的 126 例急性脑梗死患者,随机分为实验组和对照组,每组各 63 例。对照组患者给予血栓通注射液治疗;实验组患者在对照组基础上给予依达拉奉治疗。观察并比较两组患者治疗前后血清氧化低密度脂蛋白(Ox-LDL)、基质金属蛋白酶 2(MMP-2)及基质金属蛋白酶 9(MMP-9)水平的变化情况以及临床疗效。**结果:**与治疗前相比,治疗后两组患者 Ox-LDL, MMP-2 及 MMP-9 水平均下降,差异具有统计学意义($P<0.05$);与对照组相比,实验组患者 Ox-LDL, MMP-2 及 MMP-9 水平较低,差异具有统计学意义($P<0.05$);与对照组相比,实验组患者的临床疗效较高,差异具有统计学意义($P<0.05$)。**结论:**血栓通联合依达拉奉能够降低老年急性脑梗死患者氧化低密度脂蛋白(Ox-LDL)、基质金属蛋白酶 2(MMP-2)以及基质金属蛋白酶 9(MMP-9)水平,临床疗效较好。

关键词:血栓通;依达拉奉;急性脑梗死;氧化低密度脂蛋白;基质金属蛋白酶

中图分类号:R743 **文献标识码:**A **文章编号:**1673-6273(2017)17-1301-03

Effects of Xueshuantong and Edaravone on Oxidized Low Density Lipoprotein and MMPs Levels of Elderly Patients with Acute Cerebral Infarction*

REN Bei¹, ZHANG Ai-xiang¹, YANG Yun-peng¹, LI Juan¹, WANG Jing²

(1 Department of Neurology, the Fourth Hospital of Xi'an, Xi'an, Shaanxi, 710004, China;

2 Department of Neurology, the Second Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, Shaanxi, 710004, China)

ABSTRACT Objective: To investigate the effect of xueshuantong combined with edaravone on the levels of oxidized low density lipoprotein and MMPs of elderly patients with acute cerebral infarction and its clinical efficacy. **Methods:** 126 cases with acute cerebral infarction who were treated in our hospital were selected and randomly divided into the experimental group and the control group, with 63 cases in each group. The patients in the control group was treated with xueshuantong injection, and the patients in the experimental group were treated with edaravone on the basis of the control group. Then the levels of oxidized low density lipoprotein (Ox-LDL), matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) of patients in the two groups and the clinical efficacy were observed and compared before and after the treatment. **Results:** Compared with before treatment, the levels of Ox-LDL, MMP-2 and MMP-9 in the two groups decreased after treatment, and the differences were statistically significant ($P<0.05$); Compared with the control group, the levels of Ox-LDL, MMP-2 and MMP-9 in the experimental group were lower and the differences were statistically significant ($P<0.05$); Compared with the control group, the clinical effective rate in the experimental group was higher, and the difference was statistically significant ($P<0.05$). **Conclusion:** Xueshuantong and edaravone can reduce the levels of oxidation low density lipoprotein (Ox-LDL), matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) of elderly patients with acute cerebral infarction with better clinical curative effect.

Key words: Xueshuantong; Edaravone; Acute cerebral infarction; Oxidized low density lipoprotein; Matrix metalloproteinase

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

Article ID: 1673-6273(2017)07-1301-03

前言

急性脑梗死(acute cerebral infarction, ACI)又称缺血性脑卒中,是由多种因素引起的脑动脉在短期内出现狭窄和闭塞,

进而引起脑组织缺血、缺氧性坏死所造成的脑组织损伤,也是临床常见的神经内科突发急病^[1]。研究证实,高龄是急性脑梗死发生的重要危险因素^[2]。急性脑梗死发作时,坏死的脑组织导致细胞脂质过氧化以及各种缺血障碍。因此,保护脑组织对于降

* 基金项目:陕西省自然科学基金项目(20100525)

作者简介:任蓓(1983-),女,硕士研究生,主治医师,研究方向:神经内科,电话:15929951513

(收稿日期:2016-10-07 接受日期:2016-10-25)

低病死率十分重要^[3]。虽然常规的临床治疗手段能够改善脑血液循环,但对于神经功能恢复的疗效不理想^[4]。血栓通能够抗血小板聚集,防治脑缺血后造成的再灌注损伤,降低神经细胞凋亡水平^[5]。依达拉奉是强效的抗氧化以及清除羟自由基的药物,能够阻断氧自由基介导的脑损伤,抑制脑缺血,保护脑组织,同时,依达拉奉还能够改善神经功能缺损症状,保护神经^[6]。因此,本研究通过观察老年急性脑梗死患者氧化低密度脂蛋白水平, MMPs 水平及临床疗效,探讨血栓通联合依达拉奉对急性脑梗死的治疗作用,现报道如下。

1 资料与方法

1.1 临床资料

收集我院神经内科 2015 年 6 月~2016 年 6 月收治的 126 例急性脑梗死患者,随机分为实验组和对照组。其中实验组 63 例,其中男性 34 例,女性 29 例,平均年龄(67.63±1.03)岁;对照组 63 例,其中男性 36 例,女性 27 例,平均年龄(68.21±1.16)岁。患者均符合急性缺血性脑卒中诊治指南中关于急性脑梗死的诊断标准,并经 CT 及 MRI 检查确诊。所有患者除急性脑梗死外无神经系统的其他疾病,患者既往无头部外伤,无胃肠道疾病以及严重肝肾肾功能不全;所有患者实验前均未使用过实验相关药物,所有患者均签署知情同意书同意进行实验。所有患者一般资料具有可比性(P>0.05)。

1.2 方法

1.2.1 治疗方法 所有患者入院后均给予吸氧、抗血小板聚集、控制血压等基础治疗,对照组患者给予血栓通注射液(国药准字 Z45021769 生产厂家:广西梧州制药(集团)股份有限公司)450 mg+ 氯化钠注射液 250 mL,1 次/d,混合静滴;实验组患者在对照组基础上给予依达拉奉(国药准字 H20031342 生产厂家:南京先声东元制药有限公司)30 mg+ 氯化钠注射液 100 mL,2 次/d,混合静滴,连续治疗 14 d。治疗期间根据患者情况随时调整药量。

1.2.2 指标检测 治疗前后取所有患者外周静脉血 5 mL,采用 ELISA 法,检测患者血清氧化低密度脂蛋白(Ox-LDL)、基质金属蛋白酶 2(MMP-2)以及基质金属蛋白酶 9(MMP-9)水平。

1.2.3 疗效评价 治疗后对患者的治疗效果进行判定:患者根据美国卫生研究院卒中量表对患者的神经功能缺损评分(NIHSS),治愈:较治疗前降低>90%,病残程度 0 级;显效:NIHSS 评分较治疗前降低 46%~90%,病残程度 1~3 级;进步:NIHSS 评分较治疗前降低 18%~45%;无效:NIHSS 评分较治疗前降低<18%或上升。总有效率(%)=(治愈例数+显效例数+进步例数)/总例数×100%。

1.3 统计学分析

采用 SPSS 19.0 统计软件进行分析。计量数据采用 t 检验,以均数±标准差($\bar{x} \pm s$)表示;计数资料采用卡方检验,%表示。所有数据比较,以 P<0.05 认为差异有统计学意义。

2 结果

2.1 两组患者治疗前后氧化低密度脂蛋白水平比较

与治疗前相比,两组患者治疗后 Ox-LDL 水平均下降,差

异具有统计学意义(P<0.05);与对照组相比,实验组患者治疗后 Ox-LDL 水平较低,差异具有统计学意义(P<0.05),见表 1。

表 1 患者治疗前后 Ox-LDL 水平比较($\mu\text{g/L}$, $\bar{x} \pm s$)

Table 1 Comparison of the serum levels of Ox-LDL between two groups before and after treatment($\mu\text{g/L}$, $\bar{x} \pm s$)

Groups	Before treatment	After treatment
Experimental group	812.16±121.82	481.37±99.18**
Control group	829.83±145.39	577.41±103.25*

Note: Compared with before treatment, *P<0.05; compared with the control group after treatment, **P<0.05.

2.2 两组患者治疗前后基质金属蛋白酶 2(MMP-2)水平比较

与治疗前比较,两组患者治疗后血清 MMP-2 水平均下降,差异具有统计学意义(P<0.05);与对照组相比,实验组患者治疗后血清 MMP-2 水平较低,差异具有统计学意义(P<0.05),见表 2。

表 2 患者治疗前后 MMP-2 水平比较($\mu\text{g/L}$, $\bar{x} \pm s$)

Table 2 Comparison of the serum levels of MMP-2 between two groups before and after treatment($\mu\text{g/L}$, $\bar{x} \pm s$)

Groups	Before treatment	After treatment
Experimental group	172.28±71.19	71.26±31.18**
Control group	168.72±68.25	95.28±29.82*

Note: Compared with before treatment, *P<0.05; compared with the control group after treatment, **P<0.05.

2.3 两组患者治疗前后基质金属蛋白酶 9(MMP-9)水平比较

与治疗前比较,治疗后两组患者血清 MMP-9 水平均下降,差异具有统计学意义(P<0.05);与对照组相比,实验组患者治疗后血清 MMP-9 水平较低,差异具有统计学意义(P<0.05),见表 3。

表 3 治疗前后患者 MMP-9 比较($\mu\text{g/L}$, $\bar{x} \pm s$)

Table 3 Comparison of the serum levels of MMP-9 between two groups before and after treatment($\mu\text{g/L}$, $\bar{x} \pm s$)

Groups	Before treatment	After treatment
Experimental group	421.13±105.23	109.38±65.53**
Control group	433.08±99.81	198.15±81.21*

Note: Compared with before treatment, *P<0.05; compared with the control group after treatment, **P<0.05.

2.4 临床疗效比较

治疗后,实验组的治疗总有效率与对照组相比较(P<0.05),见表 4。

3 讨论

据统计^[7],我国脑梗死发病率常年居高不下,其死亡率仅次于肿瘤。急性脑梗死是病死率较高的脑血管疾病,发病率约占全部脑卒中类型的 70%,急性脑梗死是由于患者局部的脑血流突然中断造成脑组织缺血坏死,导致患者神经功能缺损的疾病的总称,患者的病因、疾病的严重程度以及转归均可不同^[8]。

表 4 患者临床疗效比较(% , $\bar{x} \pm s$)Table 4 Comparison of the clinical curative effect between the two groups(% , $\bar{x} \pm s$)

Groups	Recovery	Excellent	Effective	Invalid	Total effective rate
Experimental group	39(61.90)	16(25.40)	6(9.52)	2(3.17)	61(96.83)*
Control group	17(26.98)	21(33.33)	12(19.04)	13(20.63)	50(79.37)

Note: Compared with the control group, *P<0.05.

血栓通是由中药三七经现代工艺制成的中药注射液,具有活血化瘀的功效,其中以三七总皂苷为有效成分,还包括多种其他类型的皂苷,现代研究表明^[10],其能扩张脑血管,改善患者的脑部血液循环,有效缓解患者的症状,疗效较为显著,但其清除自由基效果弱。依达拉奉是临床常用的脑保护以及自由基清除剂,能够通过血脑屏障,其抗氧化作用和清除自由基的效果较好,可能与其抑制脂质过氧化以及炎性介质的生成有关^[11]。患者发生脑组织损伤后,血液和血管内产生毒性羟基基团,研究证实^[12],依达拉奉注射液能够清除羟基基团,且能够抑制脂质的过氧化,减少血脑屏障的破坏,改善的脑水肿症状,从而抑制神经元死亡。同时,研究证实^[13],依达拉奉不影响患者的胃肠功能、血液凝固等,对脑组织代谢的影响较小,在实验过程中,患者均未发现明显的不良反应,提示实验措施安全。

有研究表明^[14],急性脑梗死的发生与动脉粥样硬化有着较为密切的联系,脂质水平的升高与动脉粥样硬化的形成有关。而氧化低密度脂蛋白(Ox-LDL)为低密度脂蛋白氧化后的产物,其生物学性质与低密度脂蛋白相比发生了变化^[15]。在生理条件下,血管内皮的保护作用,使低密度脂蛋白不会被氧化;但血管内皮发生损伤或低密度脂蛋白水平升高,其就会被氧化。氧化低密度脂蛋白能够导致体内的炎症和应激反应,促进泡沫细胞形成,从而导致脂质的沉积加快,动脉粥样硬化形成加快,同时,氧化低密度脂蛋白还能够损伤内皮细胞,促进血小板的聚集,导致血栓的形成,最终引起急性脑梗死的发生。还有的研究表明^[16],急性脑梗死发生时,局部脑组织坏死,炎性细胞聚集导致氧自由基增多,导致低密度脂蛋白被氧化,氧化低密度脂蛋白水平升高。我们的研究表明:治疗后,两组患者的Ox-LDL水平均下降,其中实验组患者Ox-LDL水平较低。血栓通能够改善患者的脑部血液循环,联合依达拉奉注射液,保护脑细胞,能够通过血脑屏障,其抗氧化作用和清除自由基的效果较好。

金属基质蛋白酶(MMPs)对于斑块稳定具有关键作用,研究表明^[17],金属基质蛋白酶水平的升高能够造成斑块的不稳定,促进血栓的形成。金属基质蛋白酶-2(MMP-2)和金属基质蛋白酶-9(MMP-9)均为金属基质蛋白酶家族成员,能够促进血栓的形成,与缺血性脑损伤的关系密切^[18]。已有研究证实^[19,20],脑梗死患者血清中MMP-2和MMP-9的水平较高,且与患者的脑梗死面积以及意识水平呈正相关,我们的实验结果表明:治疗后,两组患者的MMP-2、MMP-9水平均下降,与对照组相比,实验组患者的MMP-2、MMP-9水平较低。提示血栓通联合依达拉奉能够改善患者脑部的血液循环,恢复正常的脂质代谢,同时,氧化低密度脂蛋白水平的下降,导致斑块的稳定性升高,也能够使金属基质蛋白的水平得以降低。

综上所述,血栓通联合依达拉奉能够降低老年急性脑梗死患者氧化低密度脂蛋白(Ox-LDL)以及基质金属蛋白酶水平。

参考文献(References)

- [1] Chen X, Bi H, Zhang M, et al. Research of Sleep Disorders in Patients with Acute Cerebral Infarction [J]. Journal of Stroke and Cerebrovascular Diseases, 2015, 24(11): 2508-2513
- [2] Hori Y S, Kodera S, Sato Y, et al. Eosinopenia as a Predictive Factor of the Short-Term Risk of Mortality and Infection after Acute Cerebral Infarction [J]. Journal of Stroke and Cerebrovascular Diseases, 2016, 25(6): 1307-1312
- [3] Hua F, Tang H, Wang J, et al. TAK-242, an antagonist for Toll-like receptor 4, protects against acute cerebral ischemia/reperfusion injury in mice[J]. Journal of Cerebral Blood Flow & Metabolism, 2015, 35(4): 536-542
- [4] Deng Q, Zhang Y, Ding H, et al. Calcific emboli originating from the brachiocephalic trunk causing acute cerebral infarction and worm-like calcification in the right middle cerebral artery[J]. Journal of Clinical Neuroscience, 2015, 22(5): 889-890
- [5] Ye L, Cai R, Yang M, et al. Reduction of the systemic inflammatory induced by acute cerebral infarction through ultraearly thrombolytic therapy [J]. Experimental and therapeutic medicine, 2015, 10 (4): 1493-1498
- [6] Lu X W. The changes and significance of serum inflammatory factors and hemodynamics in patients with acute cerebral infarction[J]. Journal of Hainan Medical University, 2016, 22(1): 103-105
- [7] Wu C, Zhao X, Zhang X, et al. Effect of Ginkgo biloba extract on apoptosis of brain tissues in rats with acute cerebral infarction and related gene expression[J]. Genet. Mol. Res, 2015, 14(2): 6387-6394
- [8] Sun Y, Xu Y, Geng L. Caspase-3 inhibitor prevents the apoptosis of brain tissue in rats with acute cerebral infarction[J]. Experimental and therapeutic medicine, 2015, 10(1): 133-138
- [9] Dong X, Liu W, Yang P. Joint detection of serum Cys-C, IL-6 and VEGF levels in patients with hypertensive acute cerebral infarction[J]. International journal of clinical and experimental medicine, 2016, 9 (6): 11645-11650
- [10] Ishikawa M, Nakayama K, Ishibashi T, et al. Case series of cerebral infarction with Trousseau's syndrome associated with malignant gynecological tumors [J]. Molecular and Clinical Oncology, 2016, 5(1): 138-142
- [11] Sun X, Berthiller J, Derex L, et al. Post-thrombolysis haemostasis changes after rt-PA treatment in acute cerebral infarct. Correlations with cardioembolic aetiology and outcome [J]. Journal of the neurological sciences, 2015, 349(1): 77-83
- [12] Son J W, Choi H, Yoo A, et al. Activation of the phosphatidylinositol 3-kinase pathway plays important roles in reduction of cerebral infarction by cilnidipine [J]. Journal of neurochemistry, 2015, 135(1): 186-193

(下转第 1317 页)

- OR-1896 elicit KATo channel-dependent dilation in resistance arteries in vivo[J]. *Pharmacol Rep*, 2013, 65(5): 1304-1310
- [10] 张晓娟,李保,王敬萍,左西孟旦、米力农和多巴酚丁胺治疗急性心力衰竭的对比研究 [J]. *中西医结合心脑血管病杂志*, 2015, (05): 631-634
- Zhang Xiao-juan, Li Bao, Wang Jing-ping. Comparison of Therapeutic Efficacy among Levosimendan, Milrinone and Dobutamine in Treatment of Acute Heart Failure [J]. *Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease*, 2015, (05): 631-634
- [11] 张松,张雪梅,高培阳. 中西医结合治疗急性心力衰竭临床疗效的 Meta 分析[J]. *中国中西医结合急救杂志*, 2015, (02): 128-132
- Zhang Song, Zhang Xue-mei, Gao Pei-yang. A Meta analysis on clinical therapeutic effects of integrated traditional Chinese and western medicine for treatment of patients with acute heart failure[J]. *Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care*, 2015, (02): 128-132
- [12] 陈丽芳. 126 例住院老年急性心力衰竭患者的病因及诱因分析[J]. *心血管康复医学杂志*, 2015, (04): 431-433
- Chen Li-fang. Analysis of causes and inducement in 126 aged patients with acute heart failure [J]. *Chinese Journal of Cardiovascular Rehabilitation Medicine*, 2015, (04): 431-433
- [13] 吴文丽. 中西医结合治疗急性心力衰竭的疗效及对血清神经激素因子的影响[J]. *现代中西医结合杂志*, 2015, (34): 3807-3809
- Wu Wen-li. Combination of traditional Chinese and Western medicine treatment of acute heart failure and effect on serum neurohormonal factor [J]. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, 2015, (34): 3807-3809
- [14] 姚瑞,孙同文,杜优优,等. 左西孟旦治疗急性心力衰竭的随机对照临床研究[J]. *中华急诊医学杂志*, 2015, 24(08): 893-896
- Yao Rui, Sun Tong-wen, Du You-you, et al. A clinical comparative study of levosimendan on patients with acutely heart failure [J]. *Chinese Journal of Emergency Medicine*, 2015, 24(08): 893-896
- [15] Sliwa K, Mayosi BM. Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa [J]. *Heart*, 2013, 99(18): 1317-1322
- [16] 郭攀,王平,孙漾丽,等. 左西孟旦治疗急性心力衰竭 62 例疗效观察 [J]. *中华全科医学*, 2013, 11(05): 680-681
- Guo Pan, Wang Ping, Sun Yang-li, et al. Clinical Observation on Levosimendan for 62 Cases of Acute Heart Failure[J]. *Chinese Journal of General Practice*, 2013, 11(05): 680-681
- [17] 陆洋,张跃明,颜永进. 左西孟旦对急性心力衰竭患者 NT-proBNP 和炎症反应标志物的影响 [J]. *海南医学院学报*, 2013, 19(11): 1515-1517, 1520
- Lu Yang, Zhang Yue-ming, Yan Yong-jin. Effect of levosimendan on the levels of NT-proBNP and inflammatory markers in patients with acute heart failure[J]. *Journal of Hainan Medical University*, 2013, 19(11): 1515-1517, 1520
- [18] 王秀芝,徐东杰. 血清微小 RNA-21-5p 表达量预测急性心力衰竭患者近期预后的价值[J]. *江苏医药*, 2015, 41(16): 1931-1933
- Wang Xiu-zhi, Xu Dong-jie. Value of serum microRNA-21-5p level in predicting short-term prognosis of patients with acute heart; failure [J]. *Jiangsu Medical Journal*, 2015, 41(16): 1931-1933
- [19] 董自平,高峰,路桂杰,等. CysC 与 NT-proBNP 对急性心力衰竭患者病情和预后的评估[J]. *河北医药*, 2015, 44(19): 2952-2954
- Dong Zi-ping, Gao Feng, Lu Gui-jie, et al. Assessment of the severity and prognosis of CysC and NT-proBNP in patients with acute heart failure [J]. *Hebei Medical Journal*, 2015, 44(19): 2952-2954
- [20] Kolseth SM, Rolim NP, Salvesen O. Levosimendan improves contractility in vivo and in vitro in a rodent model of post-myocardial infarction heart failure[J]. *Acta Physiol(Oxf)*, 2014, 210(4): 865-874

(上接第 1303 页)

- [13] Saver J L, Goyal M, Bonafe A, et al. SolitaireTM with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke[J]. *International Journal of Stroke*, 2015, 10(3): 439-448
- [14] Romano A, Biraschi F, Tavanti F, et al. Role of multidetector CT in the recognition of hyperdense middle cerebral artery sign (HMCAS) in patients with acute cerebral ischaemia: correlation with DWI-MRI sequences and clinical data [J]. *La radiologia medica*, 2015, 120(2): 222-227
- [15] Schaefer P W, Souza L, Kamalian S, et al. Limited reliability of computed tomographic perfusion acute infarct volume measurements compared with diffusion-weighted imaging in anterior circulation stroke[J]. *Stroke*, 2015, 46(2): 419-424
- [16] Di Y, He Y L, Zhao T, et al. Methylene blue reduces acute cerebral ischemic injury via the induction of mitophagy [J]. *Molecular Medicine*, 2015, 21(1): 420
- [17] Du R, Teng J F, Wang Y, et al. Clinical study of Butylphthalide combined with Xue Shuan Tong on serum inflammatory factors and prognosis effect of patients with cerebral infarction[J]. *Pakistan journal of pharmaceutical sciences*, 2015, 28(5): 1823-1827
- [18] Mawet J, Eikermann-Haerter K, Park K Y, et al. Sensitivity to acute cerebral ischemic injury in migraineurs A retrospective case-control study[J]. *Neurology*, 2015, 85(22): 1945-1949
- [19] Berkhemer O A, Fransen P S S, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke [J]. *New England Journal of Medicine*, 2015, 372(1): 11-20
- [20] Sundseth J, Sundseth A, Thommessen B, et al. Long-term outcome and quality of life after craniectomy in speech-dominant swollen middle cerebral artery infarction[J]. *Neurocritical care*, 2015, 22(1): 6-14