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## 奥德金联合奥扎格雷治疗老年脑梗死的临床疗效及机制 \*

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**摘要 目的:**研究奥德金联合奥扎格雷对脑梗死老年患者的临床疗效并探讨其治疗机制。**方法:**选择 2014 年 11 月到 2016 年 7 月我院收治的 90 例脑梗死老年患者,按随机数字表法分成对照组和试验组,各 45 例。对照组患者给予奥扎格雷治疗,试验组患者给予奥德金联合奥扎格雷治疗,两组患者均给予治疗 14 d。评价并比较两组患者临床疗效。采用美国国立卫生院神经功能缺损量表(NIHSS)评分和简易精神状态评价量表(MMSE)评分评价两组患者治疗前后神经功能损伤情况。检测并比较两组患者治疗前后血清超敏 C 反应蛋白(hs-CRP)、S100B 钙结合蛋白(S100B)、基质金属蛋白酶-8(MMP-8)及缺氧诱导因子-1α(HIF-1α)水平。记录并比较两组患者治疗过程中的不良反应发生情况。**结果:**试验组患者的总有效率为 88.89%,明显高于对照组的 68.89%(P<0.05)。治疗后,两组患者血清 hs-CRP、S100B、MMP-8 及 HIF-1α 水平均明显降低,且试验组患者降低更明显(P<0.05)。治疗后,试验组患者的 NIHSS 评分、MMSE 评分均明显优于对照组(P<0.05)。治疗过程中,对比两组的不良反应发生率,差异无统计学意义(P>0.05)。**结论:**奥德金联合奥扎格雷能够明显改善老年脑梗死患者的神经功能损伤,降低血清 hs-CRP、S100B、MMP-8 及 HIF-1α 水平,临床疗效和安全性较好,值得在临幊上推广应用。

**关键词:**奥德金;奥扎格雷;脑梗死;老年;疗效

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## Clinical Efficacy and Mechanism of Adegold Combine with Ozagrel in Elderly Patients with Cerebral Infarction\*

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**ABSTRACT Objective:** To study the clinical efficacy and the mechanism of adegold combined with ozagrel in the treatment of elderly patients with cerebral infarction. **Methods:** A total of 90 elderly patients with cerebral infarction, who were treated in Tianjin Integrated Traditional Chinese and Western Medicine Hospital from November 2014 to July 2016, were enrolled in this study and randomly divided into control group(n=45) and treatment group(n=45). The control group was treated with Ozagrel, while the treatment group was treated with adegold combined with Ozagrel. The two groups were treated for 14 days. The clinical efficacy of the two groups was evaluated and compared. The neurologic injury of the two groups before and after treatment was evaluated by the national institute of health stroke scale (NIHSS) and mini-mental state examination (MMSE). The levels of serum high-sensitivity C-reactive protein (hs-CRP), S100 calcium-binding protein B (S100B), matrix metalloproteinase-8 (MMP-8) and hypoxia-inducible factor-1α(HIF-1α) in the two groups before and after treatment were detected and compared. The adverse reactions of the two groups were recorded and compared. **Results:** The total efficacy rate(88.89%) of the treatment group was significantly higher than that(68.89%) of the control group (P<0.05). After treatment, the levels of serum hs-CRP, S100B, MMP-8 and HIF-1α in the two groups were significantly lower than before treatment, and those in the treatment group were much lower (P<0.05). After treatment, the NIHSS score and MMSE score of the experimental group were better than those of the control group (P<0.05). During the treatment, there was no significantly difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Adegold combined with Ozagrel in the treatment of elderly patients with cerebral infarction can significantly improve neurologic injury and reduce the levels of serum hs-CRP, S100B, MMP-8 and HIF-1α, with good clinical efficacy and security, which is worthy of clinical application.

**Key words:** Adejin; Ozagrel; Cerebral infarction; Elderly; Efficacy

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## 前言

脑梗死是一种发病急、进展快、致残率及死亡率高的神经内科常见心脑血管疾病<sup>[1]</sup>,研究表明发病机制与吸烟、饮酒、高血压、糖尿病、心脏病等诸多因素有关<sup>[2,3]</sup>。脑梗死主要发生在老年人群中,并且有年轻化的趋势。脑梗死的发病率随着生活节奏的加快和社会老龄化趋势的进展有逐年增加的趋势,对广大老年患者的身体健康造成严重危害<sup>[4]</sup>。因此寻找安全有效的治疗措施用于老年脑梗死患者的治疗具有重要的临床意义。奥扎格雷是一种高特异性的血栓素 A2 合成酶抑制剂,具有扩张脑血管、改善脑梗死周围血液循环,恢复神经细胞功能的作用<sup>[5]</sup>。奥德金的主要成分是小分子激活肽和磷酸肌醇寡糖,能够提高脑代谢储备力,延长脑部神经细胞的存活时间,对脑部缺血缺氧组织细胞有较好的保护作用<sup>[6]</sup>。本研究主要评价对老年脑梗死患者采用奥德金联合奥扎格雷治疗的临床效果并对其疗效机制进行探讨,现报道如下。

## 1 资料与方法

### 1.1 一般资料

本次研究所纳入的 90 例脑梗死老年病例选自我院 2014 年 11 月到 2016 年 7 月期间收治的患者,按随机数字表法分成对照组和试验组,各 45 例。纳入标准:<sup>[1]</sup> 符合全国脑血管病第 4 次会议中制定的关于脑梗死的诊断标准<sup>[7]</sup>; <sup>[2]</sup> 经脑部 CT 或 MRI 确诊为脑梗死; <sup>[3]</sup> 发病时间≤ 72 h; <sup>[4]</sup> 年龄≥ 60 岁。排除标准:<sup>[5]</sup> 既往有神经功能损伤患者; <sup>[6]</sup> 出血性脑梗死或短暂性脑缺血发作患者; <sup>[7]</sup> 近半年内有手术史患者; <sup>[8]</sup> 合并心、肝、肾等疾病患者; <sup>[9]</sup> 有精神类疾病患者; <sup>[10]</sup> 不配合治疗患者。将 90 例入选患者按随机数字表法分为对照组和试验组,各 45 例。对照组患者男 25 例,女 20 例;年龄 60-78 岁,平均年龄(65.75±6.92)岁;体重 40-70 kg,平均体重(54.19±13.37)kg;梗死部位:颞叶 9 例、基底节区 17 例、顶叶 8 例、额叶 11 例。试验组患者男 24 例,女 21 例;年龄 61-77 岁,平均年龄(65.24±5.33)岁;体重 41-69 kg,平均体重(53.32±12.81)kg;梗死部位:颞叶 10 例、基底节区 18 例、顶叶 7 例、额叶 10 例。两组患者的基线资料经比较后,结果显示无显著性差异( $P>0.05$ )。入选患者均知情同意且自愿加入本研究,并经医院伦理委员会批准。

### 1.2 治疗方法

所有患者均于分组后给予控制血糖、血压、降血脂、纠正水电解质紊乱、抗凝、营养神经等常规治疗。对照组患者在此基础上给予奥扎格雷(购自丹东医创药业有限责任公司,规格 20 mg/支,国药准字 H10970307)治疗,120 mg/次,溶解于 250 mL 的生理盐水中静脉滴注,1 次/d。试验组患者在对照组治疗的基

础上给予奥德金(购自锦州奥鸿药业有限责任公司,规格 0.2 g/支,国药准字 H20000202)治疗,0.8 g/次,用 250 mL 的生理盐水稀释,静脉滴注,1 次/d。两组患者均连续给予治疗 14 d。

### 1.3 观测指标

**1.3.1 临床疗效<sup>[8]</sup>** 临床疗效的判定依照第四次全国脑血管病会议中制定的关于脑梗死的疗效标准,分为 4 个等级,分别为:  
<sup>[1]</sup> 痊愈:美国国立卫生院神经功能缺损量表(NIHSS)评分减分率≥ 90%; <sup>[2]</sup> 显效:NIHSS 评分减分率在 80%-90% 之间; <sup>[3]</sup> 有效:NIHSS 评分减分率在 70%-80% 之间; <sup>[4]</sup> 无效:NIHSS 评分减分率≤ 70%。 NIHSS 评分减分率 = (治疗前积分 - 治疗后积分) / 治疗前积分 × 100%, 总有效率 = (痊愈例数 + 显效例数 + 有效例数) / 总例数 × 100%。

**1.3.2 神经功能损伤评价<sup>[9]</sup>** 采用 NIHSS 评分和简易精神状态评价量表(MMSE)评分评价两组患者治疗前、治疗 14 d 后神经功能损伤情况。NIHSS 量表总共分为意识水平、凝视、视野、面瘫、上肢运动、下肢运动、共济失调、感觉、语言、构音障碍及忽视症,共 11 个项目,各项目总评分越高,提示神经功能损伤程度越严重。MMSE 量表总共分为地点定向力、时间定向力、即刻记忆、注意力与计算力、延迟记忆、视空间、语言,共 7 个方面,总得分范围为 0-30 分,总得分越低提示认知功能障碍越严重。

**1.3.3 血清标志物水平** 两组患者均于治疗前、治疗 14 d 后在空腹状态下抽取肘部静脉血 5 mL,以 3000 rpm 离心 10 min 以分离血清。检测并比较两组患者血清基质金属蛋白酶-8(MMP-8)、超敏 C 反应蛋白(hs-CRP)、S100B 钙结合蛋白(S100B)及缺氧诱导因子-1α(hypoxia-inducible factor 1α, HIF-1α)水平。血清 hs-CRP 水平的检测采用免疫比浊法,所用试剂盒购自上海荣盛生物药业有限公司; 血清 S100B、MMP-8 及 HIF-1α 水平的检测采用酶联免疫吸附(ELISA)法,检测试剂盒的生产厂家均为上海哈灵生物科技有限公司,所有操作均严格依据试剂盒说明书的步骤进行。

**1.3.4 不良反应发生情况** 记录并比较两组患者治疗过程中出现的恶心呕吐、腹泻等不良情况发生率。

### 1.4 数据处理

本研究所得数据中有效率、不良反应率等计数资料以率(%)表示,采用  $\chi^2$  检验,血清因子水平以及评分等计量资料以  $(\bar{x} \pm s)$  表示并采用 t 检验,数据处理软件为 SPSS19.0,检验水准为  $\alpha=0.05$ 。

## 2 结果

### 2.1 比较临床疗效

试验组患者的总有效率较对照组患者更高( $\chi^2=5.404, P=0.020$ )。见表 1。

表 1 两组患者临床疗效比较

Table 1 Comparison of clinical efficacy between the two groups

Groups	n	Recovery	Effective	Valid	Invalid	Total effective rate
Treatment group	45	26(57.78)	6(13.33)	8(17.78)	5(11.11)	40(88.89)
Control group	45	9(20.00)	7(15.56)	15(33.33)	14(31.11)	31(68.89)

## 2.2 比较血清标志物水平

治疗前,两组患者血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平比较,差异无统计学意义( $P>0.05$ );治疗后,两组患者血清

hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平均明显低于治疗前,并且试验组患者血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平较对照组降低( $P<0.05$ ),见表 2。

表 2 两组患者治疗前后血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平的比较

Table 2 Comparison of levels of serum hs-CRP, S100B, MMP-8 and HIF-1 before and after treatment between two groups

Groups	n	Periods	hs-CRP( mg/L )	S100B( $\mu$ g/L )	MMP-8( $\mu$ g/L )	HIF-1 $\alpha$ ( ng/mL )
Treatment group	45	Before treatment	13.16± 2.89	1.26± 0.18	168.37± 12.24	1765.38± 108.95
		After treatment	5.41± 1.16**	0.22± 0.07**	40.50± 8.62**	530.46± 62.35**
Control group	45	Before treatment	12.98± 3.05	1.31± 0.20	171.62± 13.15	1748.25± 112.73
		After treatment	8.37± 1.31*	0.65± 0.11*	83.54± 9.07*	1084.34± 125.82*

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

## 2.3 比较神经功能损伤

治疗后两组患者 NIHSS 评分均明显低于治疗前,MMSE

评分均明显高于治疗前,并且相比于对照组,试验组患者的 NIHSS 评分较低而 MMSE 评分较高( $P<0.05$ )。见表 3。

表 3 两组患者治疗前后 NIHSS 评分、MMSE 评分的比较( $\bar{x}\pm s$ , 分)

Table 3 Comparison of NIHSS score and MMSE score between two groups before and after treatment ( $\bar{x}\pm s$ , scores)

Groups	n	Periods	NIHSS scores	MMSE scores
Treatment group	45	Before treatment	23.05± 4.95	15.65± 3.14
		After treatment	8.63± 1.88**	29.79± 4.20**
Control group	45	Before treatment	22.97± 5.02	16.05± 3.72
		After treatment	15.41± 2.13*	21.28± 4.05*

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

## 2.4 比较不良反应发生率

治疗过程中,对照组出现恶心呕吐症状 2 例、腹泻症状 1 例,不良反应发生率为 6.67%,试验组恶心呕吐症状 1 例,不良反应发生率为 2.22%。两组不良反应发生率比较差异无统计学意义( $\chi^2=1.047$ ,  $P=0.306$ )。

## 3 讨论

脑梗死主要是由于脑部动脉血管硬化导致管腔狭窄,甚至堵塞,引发脑组织缺血缺氧,使脑组织处于慢性低氧的状态,并形成脑动脉血栓,从而出现一系列的临床症状<sup>[10,11]</sup>。基于此,目前临床治疗脑梗死主要以早期营养受损神经、减少组织梗死面积及提高缺血缺氧神经细胞存活能力为主。研究表明<sup>[12]</sup>,脑梗死在疾病进展中,会引发血清中 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  等相关细胞因子水平的变化,降低相关细胞因子表达水平对脑梗死的治疗具有积极的意义<sup>[13]</sup>。奥扎格雷是临床常见的一种血栓素 A2 合成酶抑制剂,研究表明<sup>[14,15]</sup>,其作用有两点:<sup>[14]</sup> 抑制血栓素 A2 合成酶活性,从而血栓素 A2 合成;<sup>[15]</sup> 升高前列环素水平,从而抑制血栓形成。奥德金的成份主要有小分子激活肽、磷酸肌醇寡糖、无机盐离子、脂类、核苷酸等,能够提高脑部组织细胞对葡萄糖和氧的摄取和利用,保护受损神经细胞,改善脑部的血液循环,从而发挥保护脑组织的作用<sup>[16]</sup>。本研究探讨奥德金联合奥扎格雷对脑梗死老年患者的临床疗效及对血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平的影响<sup>[17]</sup>,研究两者联用治疗脑梗死的机制,寻求脑梗死有效的治

疗方案<sup>[18,19]</sup>。

本研究结果显示,试验组患者的总有效率明显高于对照组,差异具有统计学意义( $P<0.05$ )。提示奥德金联合奥扎格雷治疗老年脑梗死的临床疗效显著<sup>[20]</sup>。这可能是由于奥德金联合奥扎格雷,既能够极大改善脑部缺血半暗带的再灌注,还能够提高脑部组织细胞对葡萄糖和氧的摄取和利用,促进梗死组织细胞功能的恢复,对脑梗死具有较好的疗效<sup>[21,22]</sup>。本研究结果显示,治疗后,两组患者血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平均明显低于治疗前,并且试验组患者血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平均明显低于对照组,差异均具有统计学意义( $P<0.05$ )。提示奥德金联合奥扎格雷能够明显降低老年脑梗死患者血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平。hs-CRP 是常见的炎性反应标志物<sup>[23]</sup>,其在血清中的水平随着脑梗死进展明显升高。S100B 是神经胶质细胞液的重要组成成分,能够调控神经胶质细胞与神经元的相互作用,其在血清中的高表达会促进神经细胞的死亡<sup>[24]</sup>。MMP-8 是一种基质溶解素,在正常人体中呈低表达,而当脑部组织坏死时,细胞外基质遭到破坏,MMP-8 水平会显著升高<sup>[25]</sup>。HIF-1 $\alpha$  是一种转录因子,其在血清中水平提示脑梗死缺血缺氧发生的严重程度<sup>[26,27]</sup>。奥德金联合奥扎格雷能够明显促进梗死部位神经细胞的恢复,发挥保护脑组织的作用,降低患者血清中 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平,从而对脑梗死具有较好的治疗效果<sup>[28]</sup>。本研究中试验组患者治疗后各项评分均优于对照组,提示奥德金联合奥扎格雷能够明显改善老年脑梗死患者脑部神经功能损伤状况。

这是由于两种药物联合应用能够极大的促进脑部梗死部位神经细胞对葡萄糖和氧的摄取和利用,有利于神经细胞的修复和再生,从而能够改善患者脑部神经功能<sup>[29,30]</sup>。另外本研究结果显示,两组患者不良反应情况比较无明显差异( $P>0.05$ )。提示奥德金联合奥扎格雷治疗老年脑梗死的不良反应发生率较低,安全性较好。

综上所述,奥德金联合奥扎格雷能够明显改善老年脑梗死患者的神经功能损伤状况,降低血清 hs-CRP、S100B、MMP-8 及 HIF-1 $\alpha$  水平,发挥较好的临床疗效,且安全性较好,值得在临幊上推广应用。

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