·临床研究·

瑞替普酶对老年脑梗死患者的治疗效果

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【摘 要】 **目的** 探讨瑞替普酶治疗老年脑梗死的疗效及安全性。**方法** 收集2018年9月至2019年3月我院收治的老年脑梗死患者64例。研究组给予瑞替普酶治疗,对照组采用阿替普酶治疗。记录2组患者治疗后美国国立卫生研究院的卒中量表(NIHSS)评分变化和不良反应的发生情况。随访患者3个月,采用改良Rankin量表(MRS)评分衡量患者的神经功能恢复状况,并分析生存情况。采用ELISA法测定2组患者治疗前后血浆中超氧化物歧化酶(SOD)和丙二醛(MDA)含量。采用SPSS 20.0软件进行数据分析,两组间比较采用t/χ^2检验,生存分析采用Kaplan-Meier法并行Log-rank检验。**结果** 研究组患者在治疗3、7、30 d后NIHSS评分均低于对照组($P<0.05$);研究组治疗总有效率高于对照组[93.55%(29/31)和77.78%(21/27);$\chi^2=10.631$,$P=0.001$]。治疗3个月后,研究组中达到无明显残障水平患者数量显著多于对照组[62.5%(20/32)和43.75%(14/32);$\chi^2=6.816$,$P=0.009$]。研究组患者3个月生存率高于对照组($P<0.05$)。2组患者均有出血症状不良反应出现,但其不良事件发生率差异无统计学意义($P>0.05$)。2组患者治疗后的MDA浓度较溶栓前降低($P<0.05$),SOD浓度较溶栓前增高($P<0.05$)。溶栓后,研究组与对照组相比,SOD升高($P<0.05$),MDA降低($P<0.05$)。**结论** 瑞替普酶治疗可改善老年脑梗死患者预后,不良反应发生率低,其机制可能与减轻患者氧化应激反应有关。

【关键词】 老年人;脑梗死;瑞替普酶;临床疗效;安全性
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Efficacy and safety of reteplase in treatment of elderly patients with cerebral infarction

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【**Abstract**】 **Objective** To investigate the clinical efficacy of reteplase in the treatment of elderly patients with cerebral infarction. **Methods** A total of 64 elderly patients with cerebral infarction from September 2018 to March 2019 were randomly divided into study group and control group. The study group were treated with reteplase, and the control group with alteplase. After the treatment, the two groups were evaluated using National Institute of Health Stroke Scale (NIHSS), and adverse reactions were recorded. The recovery of the patients' neurological function was measured by the modified Rankin scale (MRS), and survival rate was analyzed during three months of follow-up. Serum superoxide dismutase (SOD) and malondialdehyde (MDA) were assessed by ELISA before and after thrombolytic therapy. The data were statistically analyzed by SPSS statistics 20.0. The comparison between the two groups was performed by t/χ^2 test. Survival analysis was estimated by Kaplan-Meier method and tested by Log-rank test. **Results** NIHSS score was lower in study group than in the control group ($P<0.05$) at 3 d, 7 d, 30 d of thrombolysis, and the overall effective rate was higher in the former than in the latter [(93.55%(29/31) *vs* 77.78%(21/27); $\chi^2=10.631$, $P=0.001$]. After 3 months of treatment, no obvious disability was observed in 62.5%(20/32) of the study group, which was significantly higher than 43.75%(14/32) of the control group ($\chi^2=6.816$, $P=0.009$). The 3-month survival rate of the study group was higher than that of the control group ($P<0.05$). Adverse reactions such as bleeding occurred in both groups, but with no significant difference between the two groups ($P>0.05$). Compared with before treatment, SOD significantly increased and MDA significantly decreased ($P<0.05$) in both groups after treatment. SOD increased more significantly and MDA decreased more significantly in the study group than in the control group ($P<0.05$). **Conclusion** Reteplase treatment can improve the prognosis of patients with cerebral infarction without increasing the incidence of adverse reactions, and its mechanism may be related to inhibition of oxidative stress reaction.

【**Key words**】 aged; cerebral infarction; reteplase; clinical efficacy; safety

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脑梗死是老年人群中一种常见脑血管病,超早期和早期行静脉溶栓治疗,可及时疏通血管、恢复血流,从而改善脑梗死患者的神经功能[1,2]。瑞替普酶是继阿替普酶的第三代溶栓药物,用于治疗脑梗死有良好的理论基础[3]。超氧化物歧化酶(superoxide dismutase, SOD)和丙二醛(malondialdehyde, MDA)是常用的氧化应激指标。研究表明脑梗死患者氧化应激反应水平升高(SOD 降低,MDA 升高)会加重疾病进展[4]。阿替普酶通过升高 SOD 和降低 MDA 调控氧化应激水平,改善颅内的血流循环,进而促进神经功能的恢复和疾病康复[5]。瑞替普酶对老年脑梗死患者的作用机制是否与氧化应激有关,还需进一步探究。本研究旨在探讨瑞替普酶对老年脑梗死患者的疗效以及对氧化应激反应水平的影响。

1 对象与方法

1.1 研究对象

入选 2018 年 9 月至 2019 年 3 月枣庄矿业集团中心医院神经内科脑梗死患者 64 例,随机数表法分为瑞替普酶组和阿替普酶组,每组 32 例。纳入标准:(1)起病到入院治疗<4.5 h;(2)初次发病;(3)溶栓适应证;(4)颅脑 CT 无出血或低密度影。排除标准:(1)昏迷或脑卒中症状严重;(2)发病时伴癫痫发作;(3)近 3 个月内脑卒中或心肌梗死史;(4)体检发现有内脏活动性出血或外伤(如骨折);(5)既往有颅内出血史或怀疑颅内出血;(6)CT 提示多脑叶梗死;(7)已口服抗凝药,活化部分凝血活酶时间超出正常范围 10 s 以上;(8)妊娠;(9)血小板<100×10^9/L,血糖<2.7 mmol/L;(10)收缩压>180 mmHg(1 mmHg=0.133 kPa)或舒张压>100 mmHg;(11)合并严重晚期或终末期疾病。患者均签署知情同意书。

1.2 治疗

阿替普酶组患者先静脉推注阿替普酶(德国勃林格殷格翰大药厂,国药准字 S20110052)总剂量 0.9 mg/kg 的 10%,剩余药物静脉滴注,时间>60 min。瑞替普酶组患者先将 10 MU 瑞替普酶(北京爱德药业有限公司,国药准字 S20030095)溶于 10 ml 注射用水中,缓慢静脉推注>2 min,间隔 30 min 后再次静脉推注 10 MU 瑞替普酶。2 组患者均连续治疗 2 周,观察治疗效果。

1.3 监测指标

患者治疗前常规检查血常规、血糖、心电图、凝血指标,治疗中和治疗后建立监护系统,密切监测生命体征(脉搏、呼吸和血压)和出血现象。

1.3.1 神经功能和疗效评估 记录治疗后 1、3、7、30 d 时的 NIHSS 评分及 3 个月后的 MRS 评分。治疗 30 d 后,按照 Lu 等[6]标准进行疗效评估:总有效率=(基本治愈+显著有效+有效)/总例数×100%。

1.3.2 SOD 和 MDA 水平检测 所有患者在治疗前,治疗后 1、2 和 7 d 时抽取外周静脉血 2 ml,3 500 转/min 离心 5 min。收集血清。采用酶联免疫吸附法检测 SOD 及 MDA 水平。试剂均购自武汉默沙克生物科技有限公司。

1.4 不良反应

参照欧洲急性脑卒中研究协会的判定标准[7],记录治疗过程中及治疗后出现的不良反应。

1.5 随访

通过门诊复查、探访、电话等方式随访所有患者,随访时间为 2018 年 10 月至 2019 年 6 月,以患者死亡为终点事件。无失访病例,每月随访 1 次。

1.6 统计学处理

采用 SPSS 20.0 对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验。计数资料用例数(百分率)表示,组间比较采用 χ^2 检验。生存分析采用 Kaplan-Meier 法并行 Log-rank 检验。$P<0.05$ 为差异具有统计学意义。

2 结 果

2.1 2 组患者基线资料比较

2 组患者在年龄、性别、平均发病至开始治疗时间、合并基础疾病、梗死部位、脑梗死范围等一般资料差异均无统计学意义($P>0.05$;表 1)。

2.2 2 组患者 NIHSS 评分比较

2 组患者治疗前与治疗后相比 NIHSS 评分降低($P<0.05$);在治疗前和治疗 1 d 时,研究组患者 NIHSS 评分与对照组相比均无显著性差异($P>0.05$)。在治疗 3、7 和 30 d 后,研究组患者 NIHSS 评分均低于对照组($P<0.05$;表 2)。

2.3 2 组患者近期疗效比较

治疗 30 d 后,瑞替普酶组患者基本治愈 8 例,显著有效 16 例,有效 5 例,无效 2 例。阿替普酶组患者基本治愈 6 例,显著有效 10 例,有效 5 例,无效 6 例。瑞替普酶组治疗总有效率 93.55%(29/31),高于阿替普酶组的 77.78%(21/27)($\chi^2=10.631$, $P<0.01$)。瑞替普酶组中 62.5%(20/32)患者达到无明显残障水平,高于阿替普酶组的 43.75%(14/32)($\chi^2=6.816$, $P<0.01$)。以患者死亡为终点事件,瑞替普酶组患者 3 个月生存率 90.63%(29/32),高于阿替普酶组的 71.88%(23/32)($\chi^2=3.864$, $P<0.05$)。

表1 2组患者基线资料比较

Table 1 Comparison of baseline data between two groups ($n=32$)

Item	Reteplase group	Alteplase group	t/χ^2	P value
Age(years, $\bar{x}\pm s$)	74.24±6.91	73.72±6.92	0.30	0.76
Male[n(%)]	18(56.25)	19(59.38)	0.18	0.67
Onset to treatment time(hours, $\bar{x}\pm s$)	3.21±0.52	3.31±0.94	0.54	0.59
Infarct site[n(%)]				
Basal ganglion	19(59.38)	21(65.63)	1.05	0.31
Brain stem	6(18.75)	5(15.63)	0.31	0.58
Brain lobe	5(15.63)	4(12.5)	0.40	0.53
Cerebellum	2(6.25)	2(6.25)	0.00	1.00
Cerebral infarction	6.71±1.31	6.54±1.67	0.45	0.65
Combined underlying disease[n(%)]				
Diabetes mellitus	1(3.13)	2(6.25)	1.05	0.31
Heart disease	3(9.38)	4(12.5)	0.77	0.38
Hyperlipidemia	5(15.63)	4(12.5)	0.40	0.53
Hypertension	10(31.25)	11(34.38)	0.21	0.65

表2 2组患者NIHSS评分比较

Table 2 Comparison of NIHSS scores between two groups ($n=32$, $\bar{x}\pm s$)

Group	Before treatment	1 d after treatment	3 d after treatment	7 d after treatment	30 d after treatment
Reteplase	12.01±2.92	10.28±3.25*	7.34±2.36$^{***\#}$	6.12±1.67$^{***\#\#\#}$	2.26±1.21$^{***\#\#\#}$
Alteplase	11.99±2.43	11.33±4.19	8.94±2.49***	7.96±2.18***	3.96±1.96***

NIHSS: national institutes of health stroke scale. Compared with before treatment, $^{*}P<0.05$, $^{***}P<0.001$; compared with alteplase group, $^{\#}P<0.05$, $^{\#\#\#}P<0.001$.

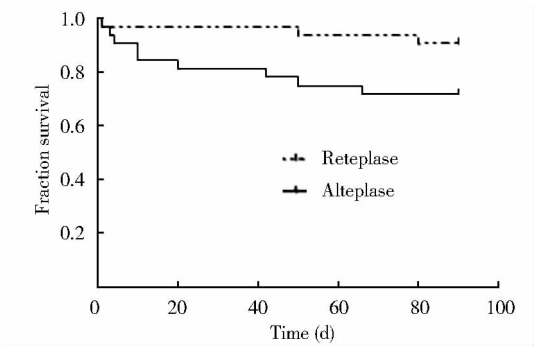

图1 2组患者的Kaplan-Meier生存分析

Figure 1 Kaplan-Meier survival analysis of two groups of patients

2.4 不良反应

瑞替普酶组出现症状性颅内出血2例,非症状性颅内出血2例,颅外出血3例,均为非严重性出血。阿替普酶组出现症状性颅内出血1例,非症状性颅内出血1例,颅外出血4例,也均为非严重性出血。瑞替普酶组不良反应发生率为21.88%(7/32),与阿替普酶组[18.75%(6/32)]相比,差异无统计学意义($\chi^2=0.276$, $P=0.599$)。

2.5 2组患者SOD和MDA水平比较

2组患者治疗前SOD、MDA浓度比较差异无统计学意义($P>0.05$)。2组患者治疗后MDA水平较治疗前降低($P<0.05$),SOD水平较治疗前增高($P<0.05$),瑞替普酶组相比阿替普酶组SOD水平显著升高($P<0.05$),MDA水平显著降低($P<0.05$;表3)。

3 讨 论

阿替普酶是一种纤维蛋白特异性溶栓剂,能选择性地将赖氨酸残基与血栓表面的纤维蛋白结合形成复合物,将血栓部位无活性的纤溶酶原转变为纤溶酶,迅速溶解血栓[8]。超早期和早期阿替普酶静脉溶栓治疗脑梗死已成为各国脑梗死治疗指南推荐的首选[8-9]。瑞替普酶是在阿替普酶的分子结构上进行了修饰,能提高溶栓效果和速度[3],临床结果表明在患者使用瑞替普酶的溶栓再通率优于阿替普酶[10]。

目前研究发现年龄是影响阿替普酶治疗效果的独立预测因素之一,高龄患者可以在静脉溶栓治疗中获益,但获益程度低于低龄组患者[11]。但高龄患者使用瑞替普酶的效果还需进一步的探究。本研究以老年脑梗死患者作为研究对象,发现瑞替普酶近期疗效高于阿替普酶,且瑞替普酶组患者3个月生存率高于阿替普酶组。这与Bhatnagar等[12]研究结果一致,提示老年脑梗死患者进行瑞替普酶治疗是有效的。老年患者器官退化、总体预后差,临床结果表明静脉溶栓治疗后症状性颅内出血比例增高[13]。但本研究发现瑞替普酶治疗组和阿替普酶治疗组患

表 3 2 组患者 SOD 和 MDA 水平比较

Table 3 Comparison of SOD and MDA levels between two groups ($n=32$, $\bar{x}\pm s$)

Group	SOD				MDA			
	Before treatment	1 d after treatment	2 d after treatment	7 d after treatment	Before treatment	1 d after treatment	2 d after treatment	7 d after treatment
Reteplase	72.34±19.56	91.25±12.27$^{***\#}$	97.43±16.71$^{***\#}$	106.59±24.83$^{***\#}$	10.08±1.53	7.01±1.82$^{***\#\#}$	6.12±1.09$^{***\#\#\#}$	4.98±1.16$^{***\#\#\#}$
Alteplase	72.13±18.26	82.23±19.72**	85.36±21.56***	92.41±21.06***	10.23±1.31	8.49±1.98***	7.42±1.04***	6.72±1.29***

SOD: superoxide dismutase; MDA: malondialdehyde。Compared with before treatment, $^{**}P<0.01$, $^{***}P<0.001$; compared with alteplase group, $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$.

者均出现出血症状,且无显著差异,提示在老年脑梗死患者进行瑞替普酶治疗是安全的。目前研究表明,氧化应激是老年脑梗死患者中神经细胞损伤的基本机制之一[4]。MDA 自由基作用于脂质发生过氧化反应的终产物。SOD 是机体内重要的抗氧化酶。卢志刚等[14]和 Li 等[15]研究结果表明,在急性脑梗死患者中升高 SOD 含量和降低 MDA 含量可以减少脑细胞损伤,促进神经功能的恢复。这与本研究结果一致,提示瑞替普酶可降低脑梗死患者的氧化应激水平,发挥保护作用,促进疾病康复。

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