

· 临床研究 ·

高血糖对急性缺血性脑卒中老年患者溶栓后梗死体积与院内预后的影响

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【摘要】目的 了解就诊时血糖升高与急性缺血性脑卒中老年患者接受重组组织型纤溶酶原激活剂(rt-PA)溶栓后脑梗死体积变化及院内(发病后1周内)预后的关系。**方法** 发病后3h接受rt-PA的急性缺血性卒中老年患者,按照就诊血糖分为高血糖组与正常血糖组,采用磁共振检查评价溶栓各时间点血管再通率、脑梗死体积变化,并评价各时间段的国立卫生研究院卒中量表(NIHSS)评分及预后指标。**结果** 共44例纳入本研究,其中高血糖组24例,正常血糖组20例。溶栓即刻高血糖组患者梗死体积与正常血糖患者相比无明显差异[(29.5±56.2) vs (28.3±61.7), $P=0.90$], NIHSS评分明显增高[(17.7±6.6) vs (12.9±6.3), $P<0.01$];高血糖患者溶栓24h后血管再通率与出血转化率相同;发病后24h及1周,高血糖患者脑梗死体积更大[(121.7±101.1) vs (68.8±85.4), $P=0.03$; (170.8±163.9) vs (92.5±113.6), $P=0.02$], NIHSS评分更高[(14.3±6.9) vs (8.6±5.1), $P<0.01$; (8.8±7.4) vs (4.3±3.9), $P<0.01$],发病后1周,高血糖患者的不良预后的比例比正常血糖者明显升高(42% vs 15%, $P=0.05$)。**结论** 就诊时高血糖对脑卒中老年患者rt-PA溶栓血管再通率及安全性无明显影响,高血糖与溶栓后院内梗死延展及预后不良明显相关。

【关键词】 高血糖症;卒中;血栓溶解疗法;预后;老年人

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Effect of hyperglycemia on infarct volume and in-hospital outcome in elderly patients with acute ischemic stroke after thrombolysis

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【Abstract】Objective To investigate the relationship of admission hyperglycemia with changes in infarct volume and in-hospital outcome (within 1 week after onset) in the elderly patients with acute ischemic stroke after the treatment of recombinant tissue plasminogen activator (rt-PA). **Methods** All consecutive elderly patients suffering from acute ischemic stroke and treated with rt-PA within 3h after onset in our hospital from 2010 to 2013 were enrolled in the study. They were divided into hyperglycemic group and normoglycemic group according to their blood glucose levels at admission. The recanalization and infarct volume at different time points after onset were evaluated with magnetic resonance scanning. The National Institute of Health Stroke Scale (NIHSS) scores of different time points were also evaluated and compared between the 2 groups. **Results** There were totally 44 patients enrolled in the study, and 24 of them had admission hyperglycemia. There was no difference in initial infarct volume between the normoglycemic and hyperglycemic groups [(29.5±56.2) vs (28.3±61.7), $P=0.90$]. However, hyperglycemic patients had higher admission NIHSS scores [(17.7±6.6) vs (12.9±6.3), $P<0.01$]. No difference was seen in the recanalization and hemorrhage rate between the 2 groups at 24h after onset. In 24h and 7d after onset, hyperglycemic patients had larger stroke volume [(121.7±101.1) vs (68.8±85.4), $P=0.03$; (170.8±163.9) vs (92.5±113.6), $P=0.02$], and higher NIHSS scores than normoglycemic patients [(14.3±6.9) vs (8.6±5.1), $P<0.01$; (8.8±7.4) vs (4.3±3.9), $P<0.01$]. Hyperglycemic patients also had higher rate of poor prognosis at 7d after onset than normoglycemic group patients (42% vs 15%, $P=0.05$). **Conclusion** Admission hyperglycemia does not interfere the early recanalization and safety of rt-PA thrombolysis, but it is associated with in-hospital infarct volume expansion and poor outcome in the elderly acute ischemic stroke patients.

【Key words】 hyperglycemia; stroke; thrombolytic therapy; prognosis; elderly

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急性缺血性脑卒中患者发病早期易发生应激性血糖升高,且使患者梗死范围更大,预后更差^[1,2]。发病后3h的急性缺血性卒中患者如果接受重组组织型纤溶酶原激活剂(recombinant tissue plasminogen activator, rt-PA)溶栓治疗,其神经功能能够获得明显的改善^[3],我国《指南》^[4]推荐方案为0.9mg/kg,总剂量<90mg。老年缺血性卒中患者其病情较年轻患者明显加重,溶栓治疗后出血并发症明显增高;为了解高血糖是否与老年患者溶栓治疗的安全性及预后指标密切相关,本研究选取了2010~2013年就诊海军总医院、于发病3h内接受rt-PA溶栓的缺血性脑卒中老年患者,对就诊时血糖水平与患者溶栓后血管再通、脑梗死体积变化之间的关系进行了分析。

1 对象与方法

1.1 对象与分组

2010年1月至2013年12月,于海军总医院经急诊颅脑磁共振成像(magnetic resonance imaging, MRI)检查确诊急性缺血性卒中拟行溶栓治疗的老年患者,纳入标准:(1)65岁<年龄<80岁,溶栓前美国国立卫生研究院卒中量表(National Institute of Health Stroke Scale, NIHSS)评分4~26分;(2)就诊时间为发病后<3h;(3)无rt-PA溶栓禁忌证;(4)溶栓后即刻,磁共振血管成像(magnetic resonance angiography, MRA)检查证实存在明确颅内动脉闭塞。所有患者入院当时采静脉血测血糖水平,根据如下标准分为高血糖组与血糖正常组。高血糖组:(1)空腹>4h,血糖>7.1mmol/L;(2)空腹2~4h,血糖>7.8mmol/L;(3)任何时间血糖>11.1mmol/L^[2]。

1.2 试验方法及指标采集

所有患者入院时采集如下指标。(1)一般指标:性别,年龄,发病时间,进餐时间;(2)既往病史:高血压、糖尿病、高脂血症、心房颤动、吸烟史等;(3)临床指标:就诊时血糖、血生化、血常规指标及NIHSS评分;(4)影像学指标:所有患者于溶栓后即刻及发病后24h接受颅脑MRI、弥散加权成像(diffusion weighted imaging, DWI)、MRA检查;溶栓后7d行液体衰减反转恢复(fluid attenuated

inversion recovery, FLAIR)检查。

1.3 溶栓治疗临床效果判断

溶栓治疗:按照我国《指南》要求,患者就诊时经急诊颅脑CT排除脑出血后,立即给予rt-PA0.9mg/kg静滴,总剂量不超过90mg^[4]。临床效果判断:(1)梗死动脉再通情况,通过发病后24h MRA进行判断;(2)脑梗死体积变化情况,通过比较发病后不同时间点的MRI的梗死体积判断;(3)神经功能改善情况,通过比较不同时间点NIHSS评分进行判断;NIHSS评分较入院时降低 ≥ 4 分,评价为症状改善,评分增加 ≥ 4 分,评价为症状恶化。

1.4 统计学处理

采用SPSS13.0软件进行数据分析。组间计数资料比较采用 χ^2 分析,由于梗死体积指标不服从正态分布,故两组间差异采用非参数检验Mann-Whitney U检验,计量资料采用均数 $\pm$ 标准差表示,组间比较采用t检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者溶栓前一般情况比较

被纳入本研究的44例患者溶栓后即刻MRA证实明确的颅脑动脉闭塞并完成入院后7d的随访;其中男性21名;年龄为(71.5 $\pm$ 10.6)岁;其中高血糖组24例,正常血糖组20例。两组患者年龄、性别差异无统计学意义,高血糖组糖尿病患者比例明显增高,NIHSS评分明显增高;其余指标无差异,两组患者溶栓前各项临床指标见表1。

2.2 两组患者溶栓后影像学指标及临床疗效的比较

我们比较了高血糖组与正常血糖组患者溶栓后不同时间点的影像学指标、NIHSS评分及预后的差异。结果显示,高血糖患者接受rt-PA溶栓后,其罪犯血管分布、溶栓后血管再通率及出血转化率与正常血糖者无明显差异,但是发病后24h及1周的脑梗死体积明显增加,NIHSS评分明显高于正常血糖患者,发病后24h症状改善率与正常血糖者无明显差异;发病后1周预后不良(恶化及死亡)患者的比例明显高于正常血糖患者(10 vs 3, 42% vs 15%, $P = 0.05$, 表2)。

表1 两组患者基线特征比较
Table 1 Comparison of baseline characteristics between normoglycemic and hyperglycemic groups

Item	Normoglycemic group (n = 20)	Hyperglycemic group (n = 24)
Male[n(%)]	10 (50)	11 (46)
Age(years, $\bar{x} \pm s$)	71 $\pm$ 10	73 $\pm$ 11
BMI(kg/m ² , $\bar{x} \pm s$)	26.3 $\pm$ 5.8	25.9 $\pm$ 6.7
Past history		
Hypertension[n(%)]	13 (65)	15 (63)
Hyperlipidemia[n(%)]	4 (20)	6 (25)
Diabetes[n(%)]	3 (15)	5 (21)
Atrial fibrillation[n(%)]	6 (30)	6 (25)
Smoking[n(%)]	7 (35)	8 (33)
Clinical characteristics at admission		
Thrombolysis time after onset(min, $\bar{x} \pm s$)	148.5 $\pm$ 32.9	154.1 $\pm$ 37.3
Blood pressure (mmHg, $\bar{x} \pm s$)	158.2 $\pm$ 17.8	160.1 $\pm$ 20.9
Admission blood glucose (mmol/L, $\bar{x} \pm s$)	6.6 $\pm$ 0.5	9.7 $\pm$ 2.3**
NIHSS scores($\bar{x} \pm s$)	12.9 $\pm$ 6.3	17.7 $\pm$ 6.6**

BMI: body mass index; NIHSS: National Institutes of Health Stroke Scale. Compared with normoglycemic group, ** $P < 0.01$. 1mmHg=0.133kPa

表2 溶栓后两组患者影像学及临床预后的比较
Table 2 Imaging and clinical outcomes of two groups after thrombolysis

Item	Normoglycemic group (n = 20)	Hyperglycemic group (n = 24)	P
At time of thrombolysis			
Occluded artery			
ICA[n(%)]	6 (30)	9 (38)	0.6
M1[n(%)]	9 (45)	10 (42)	0.82
M2[n(%)]	5 (25)	5 (21)	0.74
Stroke volume (cm ³ , $\bar{x} \pm s$)	28.3 $\pm$ 61.7	29.5 $\pm$ 56.2	0.9
At 24 hours after onset			
Recanalization [n(%)]	10 (50)	10 (42)	0.58
Stroke volume (cm ³ , $\bar{x} \pm s$)	68.8 $\pm$ 85.4	121.7 $\pm$ 101.1	0.03
Hemorrhage[n(%)]	6 (30)	8 (33)	0.68
NIHSS scores ($\bar{x} \pm s$)	8.6 $\pm$ 5.1	14.3 $\pm$ 6.9	< 0.01
Symptom improved [n(%)]	12 (60)	12 (50)	0.51
Symptom worsen [n(%)]	1 (5)	3 (13)	0.39
At 7 days after onset			
Stroke volume (cm ³ , $\bar{x} \pm s$)	92.5 $\pm$ 113.6	170.8 $\pm$ 163.9	0.02
NIHSS scores($\bar{x} \pm s$)	4.3 $\pm$ 3.9	8.8 $\pm$ 7.4	< 0.01
Symptom improved [n(%)]	14 (70)	12 (54)	0.18
Symptom worsen [n(%)]	2 (10)	6 (21)	0.32
Mortality[n(%)]	1 (5)	4 (15)	0.22
Worsen and Mortality [n(%)]	3 (15)	10 (41)	0.05

ICA: internal carotid artery; NIHSS: National Institute of Health Stroke Scale

3 讨论

血糖升高在急性卒中患者发病初期极为常见, 目前多项临床研究证实, 血糖升高是急性卒中患者不良预后的危险因素^[5-9]。

本试验结果显示, 高血糖与正常血糖老年患者相比, 在接受溶栓前, 除合并糖尿病的比例明显增高外, 既往合并高血压、高脂血症、心房颤动以及吸烟史的比例与正常血糖者无明显差异, 且入院时影像学检查显示, 高血糖患者的梗死相关血管构成及梗死体积无明显差异, 但是其溶栓前NIHSS评分明显高于正常血糖患者。该结果提示, 急性卒中后血糖升高老年患者在同等缺血负荷的情况下, 其神经系统功能丧失情况更明显; 可见, 在急性缺血性卒中患者就诊时, 通过测定其血糖水平, 有利于对患者进行危险分层, 便于发现高危患者, 进一步采取针对性的强化治疗以改善预后。

我们的研究也发现, 接受rt-PA溶栓时, 高血糖患者症状发作后24h后的血管再通率与正常血糖老年患者并无区别, 且其溶栓后24h发生出血转化的比例亦无明显增加。这个结果提示我们, 对于急性缺血性卒中老年患者, 高血糖水平并不影响rt-PA的溶栓再通效果, 也不会造成出血并发症的明显增加, 对于急性卒中后出现血糖升高的高危老年患者, 应积极按照《指南》采取rt-PA溶栓治疗, 以改善患者的预后。

再者, 在同等溶栓成功率的情况下, 在溶栓后不同时间点, 高血糖老年患者的梗死体积均明显增加, NIHSS评分显著高于正常血糖患者; 发病后24h, 高血糖患者的预后不良趋势并不显著, 但是发病后1周高血糖患者与正常血糖患者相比, 预后的差异显著, 表现为高血糖老年患者脑梗死体积明显增加, 症状恶化率及死亡率明显升高; 这提示, 即使采取了同样有效的再灌注治疗, 高血糖水平仍然是梗死体积增加的危险因素, 高血糖水平可能对缺血状态下的脑组织具有额外附加的损害作用。既往多项动物实验研究也证实, 高血糖水平能够增加半暗区无氧酵解, 缺血脑组织通过无氧酵解产生大量乳酸, 造成细胞内酸中毒, 促进自由基形成、细胞内钙超载, 损害线粒体功能, 促进并加剧缺血脑损伤。另一方面在应激性高血糖情况下, 红细胞变形能力下降、聚集性增高、纤维蛋白增加、血液黏度增高, 从而出现明显的高凝状态, 不利于急性期侧支循环的形成甚至加重梗死延展^[10-15]。这提示对于急性缺血性卒中就诊时血糖升高的老年患者, 强化改善缺

血区循环、保护神经功能等治疗,可能有利于改善他们的预后。

我们通过本研究证实,急性缺血性卒中老年患者就诊时血糖升高,对发病后3h内rt-PA溶栓的成功率及出血并发症无明显影响,但高血糖老年患者溶栓后梗死面积的增加更为显著,不良预后的发生率随时间延长而增加。对于就诊时血糖升高的急性缺血性卒中老年患者,应积极按照指南要求进行溶栓治疗,改善缺血区的供血,同时应进一步强化改善脑供血、神经细胞保护等治疗,以改善患者的预后。

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