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小剂量阿替普酶治疗急性脑梗死患者的临床疗效及安全性评价*

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摘要 目的:探讨急性脑梗死患者静脉溶栓使用小剂量(0.6 mg/kg)阿替普酶的临床疗效及安全性。**方法:**将2016年1月至2019年12月我院神经内科收治的溶栓时间窗内40例急性脑梗死患者随机分为标准剂量组(0.9 mg/kg)和小剂量组(0.6 mg/kg),每组20例,分别在溶栓前、溶栓后1小时对患者进行美国国立卫生研究院卒中量表(NIHSS)评分,溶栓前和溶栓后24小时做头颅CT排除脑出血,密切监测不良反应。**结果:**标准剂量组有效率为80.00%,小剂量组有效率为75.00%,两组比较差异无统计学意义($P>0.05$)。治疗前两组NIHSS评分比较差异无统计学意义($P>0.05$),治疗后两组NIHSS评分均降低,与治疗前相比差异有统计学意义($P<0.05$),治疗后两组NIHSS评分差异无统计学意义($P>0.05$)。标准剂量组总不良反应发生率为40.00%,高于小剂量组的20.00%,差异无统计学意义($P>0.05$)。**结论:**阿替普酶可有效改善急性脑梗死患者的神经功能,小剂量(0.6 mg/kg)与标准剂量(0.9 mg/kg)溶栓效果相当,安全性较好,出血事件发生率较低,可根据患者情况酌情选用小剂量。

关键词:阿替普酶;静脉溶栓;急性脑梗死;不良反应;剂量;神经功能

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Clinical Efficacy and Safety of Low Dose Alteplase in the Treatment of Patients with Acute Cerebral Infarction*

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ABSTRACT Objective: To investigate the clinical efficacy and safety of low-dose (0.6 mg / kg) alteplase in patients with acute cerebral infarction. **Methods:** 40 acute cerebral infarction patients within thrombolysis time window admitted in neurology department of our hospital from January 2016 to December 2019 were randomly divided into standard dose group (0.9 mg / kg) and small dose group (0.6 mg / kg), there were 20 cases in each group. National Institutes of Health Stroke Scale (NIHSS) scores were assessed before and 1 hour after thrombolysis. CT scan was performed before and 24 hours after thrombolysis to exclude cerebral hemorrhage and close monitor of adverse reactions. **Results:** The effective rate was 80.00% in standard dose group and 75.00% in small dose group, there was no significant difference between the two groups ($P>0.05$). There was no significant difference in NIHSS scores between the two groups before treatment ($P>0.05$). NIHSS scores in both groups were decreased after treatment, the difference was statistically significant compared with before treatment ($P<0.05$). There was no significant difference in NIHSS score between the two groups after treatment ($P>0.05$). The total incidence of adverse reactions was 40.00% in the standard dose group, which was higher than 20.00% in the small dose group, the difference was no statistically significant ($P>0.05$). **Conclusion:** Alteplase can effectively improve the neurological function of patients with acute cerebral infarction. The thrombolytic effect of low dose (0.6 mg / kg) is similar to that of standard dose (0.9 mg / kg), the safety is good and the incidence of bleeding is low. Small dose can be selected according to the patient's condition.

Key words: Alteplase; Intravenous thrombolysis; Acute cerebral infarction; Adverse reaction; Dose; Neurological function

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前言

我院成立卒中中心,迅速识别疑似脑卒中患者,通过CT/MRI检查首先判断是缺血性或出血性卒中及其严重程度,并第一时间救治,临床实际中约有60%-80%的卒中为急性脑梗死,静脉溶栓治疗是目前最重要的恢复血流措施,重组组织型纤溶酶原激活剂是主要的溶栓药,可以使血栓中的纤维蛋白溶解,从而使被阻塞的血管再通^[1,2],时间窗为4.5小时,推荐阿替普酶标准剂量为0.9 mg/kg。近年来,越来越多的研究提示小剂量阿替普酶(0.6 mg/kg)在东南亚人群中具有优势,日本J-ACT研究显示小剂量0.6mg/kg具有相似的临床疗效且降低溶栓后脑出血转化风险^[3],中国台湾TTT-AIS研究显示标准剂量组溶栓后脑出血转化风险是小剂量组的2倍,对于70岁以上的老年患者,推荐使用0.6 mg/kg^[4]。本文对我院使用小剂量阿替普酶治疗急性脑梗死的临床疗效和安全性进行评价,现作以下报道。

1 资料与方法

表1 两组患者一般情况和治疗前NIHSS评分

Table 1 General conditions and NIHSS scores before treatment in patients of the two groups

Index	Standard dose group(n=20)	Small dose group(n=20)	t/ χ^2	P
Age(year)	64.00±9.53	69.85±11.90	1.716	0.094
Gender	15/5	11/9	1.758	0.185
Hypertension and hyperlipidemia	13	15	0.476	0.490
Coronary heart disease	5	8	1.026	0.311
Diabetes	7	7	0.000	1.000
Hyperhomocysteinemia	1	3	1.111	0.292
NIHSS scores(score)	9.80±5.46	10.10±5.62	0.220	0.827

1.2 方法

阿替普酶小剂量组0.6 mg/kg按照体重计算总量,最大剂量为60 mg,第一步是静脉注射总剂量的1/10,注射时间应控制在1 min内,剩下的剂量使用0.9%氯化钠注射液溶解,微泵输注1h;阿替普酶标准剂量组0.9 mg/kg按照体重计算总量,最大剂量为90 mg,治疗方法同小剂量组。用药期间和24小时内密切观察患者情况。

1.3 观察指标

(1)神经功能评价:分别在溶栓前、溶栓后1小时,由同一位高资历神经科医师对患者进行NIHSS评分以减少数据误差,溶栓前和溶栓后24小时做头颅CT进行影像学评价排除颅内出血。NIHSS量表共有15个条目,11项内容,各条目分为3~5个等级,评分0~42分,患者神经功能缺损程度越严重则得分越高。(2)临床疗效^[5]:显效:溶栓后1小时,NIHSS评分减少>80%;有效:溶栓后1小时,NIHSS评分减少20%~80%;无效:溶栓后1小时,NIHSS评分减少20%以下或加重;总有效率=(显效+有效)/总例数×100%。(3)安全性和病程进展:溶栓前做头颅CT排除颅内出血,溶栓期间和溶栓后24小时密切监测生命体征,溶栓后24小时做头颅CT进行影像学评价是否出现溶栓后脑出血转化(HT),病程中病情变化及时做相关检

1.1 一般资料

选取2016年1月至2019年12月在我院神经内科接受阿替普酶静脉溶栓的急性脑梗死患者40例,符合《中国急性缺血性脑卒中诊治指南2014》诊断标准^[6],纳入标准:^①发病时间≤4.5小时;^②年龄18-80岁;^③CT排除脑出血;^④既往无明显神经功能缺损;^⑤凝血功能和血小板计数正常;^⑥美国国立卫生研究院卒中量表(NIHSS)^[6]评分≥5分。排除标准:^①高血压,收缩压≥180 mmHg或舒张压≥100 mmHg;^②血糖≤2.7 mmol/L;^③既往有颅内出血史;^④既往脑梗死病史或心肌梗死病史;^⑤活动性内出血、外伤骨折、颅脑外伤史;^⑥伴有精神性疾病、意识障碍等无法完成检查。患者家属均知悉适应症和溶栓风险,且签署同意书。本研究经医院伦理委员会审核通过。40例患者均在溶栓时间窗4.5小时以内,按随机数字表法分为标准剂量组(0.9 mg/kg)和小剂量组(0.6 mg/kg)各20例,两组在NIHSS评分、年龄、性别、危险因素方面比较差异无统计学意义($P>0.05$),如表1所示。

查,观察并记录其它不良事件发生时间和处理过程及结果。

1.4 统计学分析

采用SPSS 23.0软件进行数据分析。计数资料采用比或率表示,以 χ^2 检验。计量资料用均值±标准差($\bar{x} \pm s$)表示,组间比较采用成组t检验,组内比较采用配对t检验。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 神经功能评价

标准剂量组和小剂量组阿替普酶静脉溶栓后1小时NIHSS评分与溶栓前相比均有明显降低($P<0.05$),溶栓前、溶栓后1小时两组NIHSS评分比较差异均无统计学意义($P>0.05$),见表2。

2.2 临床疗效评价

标准剂量组总有效率为80.00%,小剂量组总有效率为75.00%,两组比较差异无统计学意义($P>0.05$),见表3。

2.3 不良反应监测

40例急性脑梗死患者不良反应见表4,溶栓后24小时行头颅CT检查,标准剂量组出现2例HT,小剂量组出现1例HT,两组总不良反应发生率比较差异无统计学意义($P>0.05$)。

表 2 两组患者溶栓前和溶栓后 1 小时 NIHSS 评分($\bar{x} \pm s$, 分)Table 2 NIHSS scores of patients in the two groups before and 1 hour after thrombolysis ($\bar{x} \pm s$, score)

Groups	NIHSS scores	
	Before thrombolysis	1 hour after thrombolysis
Standard dose group(n=20)	9.80±5.46	6.45±4.66*
Small dose group(n=20)	10.10±5.62	6.75±4.61*
t	0.220	0.399
P	0.827	0.692

Note: compared with before thrombolysis, * $P < 0.05$.

表 3 两组患者临床疗效评价

Table 3 Clinical efficacy evaluation of the two groups

Groups	Excellent	Valid	Invalid	Total effective rate
Standard dose group(n=20)	3	13	4	16(80.00%)
Small dose group(n=20)	4	11	5	15(75.00%)
χ^2				0.421
P				0.810

表 4 两组不良反应情况比较

Table 4 Comparison of adverse reactions between the two groups

Groups	HT	Bleeding gums	The lingual bleeding	Blood-stained sputum	The incidence of total adverse reactions
Standard dose group(n=20)	2	3	2	1	8(40.00%)
Small dose group(n=20)	1	3	0	0	4(20.00%)
χ^2					2.250
P					0.522

2.4 病程转归

标准剂量组有 2 例患者病情进展为大面积脑梗死,小剂量组有 2 例进展为大面积脑梗死,两组各出现 1 例卒中后抑郁患者,医嘱予氟西汀治疗。

3 讨论

急性脑梗死灶主要包括中心坏死区和其周边的缺血半暗带,中心坏死区在血管闭塞后 10 min 内就会出现坏死,缺血半暗带因为局部存在较多脑血流,在一定时间内极少出现梗死,急性溶栓治疗挽救缺血半暗带,使可逆的受损区域能快速再灌注,进而达到恢复患者神经功能的目的^[8-10]。急性脑梗死 6 小时半暗带逐渐缩小,超过 24 小时则半暗带消失,因此在时间窗内尽早溶栓效果越好^[11]。阿替普酶为在体外采用 DNA 重组技术获得的纤溶酶激活剂,特异性较强,可将血栓表面的纤维蛋白转化为纤溶酶,进而溶解血栓,常用于治疗急性脑梗死、急性心肌梗死、急性大面积肺栓塞等^[12,13]。用于治疗急性脑梗死的剂量欧洲人群为 0.9 mg/kg 的标准剂量,欧洲人群与亚洲人群在体质、种族、经济水平、血管危险因素等方面存在差异,有研究表明标准剂量可能会增加出血风险和 3 个月的病死率,特别是对于高龄患者,而 0.6 mg/kg 可降低颅内出血风险而疗效相当,选择治疗方案时首先考虑将早期危害降至最低,如 HT 的发生率^[14,15]。本研究分析小剂量组(0.6 mg/kg)阿替普酶对急性脑梗

死患者神经功能和临床疗效的影响,小剂量组与标准剂量组溶栓 1 小时后神经功能改善明显,且两组改善效果相当。另外,本研究结果显示,小剂量与标准剂量治疗者临床疗效相当。两组共出现 12 例不良事件,但组间比较无差异。

阿替普酶可显著降低急性脑梗死患者的病死率和致残率,但可能增加 HT,溶栓 HT 的发生率为 3%-9%^[16],在本研究中,HT 为 7.50%(3/40),3 例 HT 均在溶栓 24 小时内发生,标准剂量组的 2 例 HT 均为高龄患者。两组各出现 3 例牙龈出血,可能是应用阿替普酶后凝血功能异常所致,也可能与牙龈病变所致牙龈充血肿胀有关。HT 是静脉溶栓最严重的并发症,通常发生在静脉溶栓治疗后 24 小时内^[17]。静脉溶栓出血转化危险因素包括:① 溶栓前的 NIHSS 评分是静脉溶栓治疗后导致脑出血的独立危险因素,NIHSS 评分越高病情越严重,预示溶栓效果不佳及预后不良^[18];② 心源性脑梗死,房颤导致血栓形成,栓子脱落后形成心源性栓塞,一般梗死面积较大会增加半暗带区出血风险^[19];③ 起病-溶栓时间越长脑组织受不良影响就会越严重,提高 HT 的发生率,3~4.5 小时内溶栓 HT 发生率高于 3 小时内;④ 高龄是急性脑梗死的不良转归因素,年龄大于 70 岁患者溶栓后出血转化风险较高^[20],这可能与老年人脑淀粉样血管病与脑白质疏松有关;⑤ 溶栓前基线血压增高^[21],在溶栓前和溶栓 24 小时内控制好血压,将收缩压控制在 140~159 mmHg,开始 2 小时内每 15 分钟测量 1 次血压,前 6 小时内每 30 分钟

测量1次,24小时内每1小时测量1次,平稳血压。

该研究中有4例患者出现了病情加重,复查CT为大面积脑梗死,予丁苯酞和血小板抑制劑治疗。进展性脑梗死指的是脑梗死发生6h~7d内,患者的神经功能缺损症状处于进行性发展状态,原发血栓逐渐增加或引发新发病灶形成,发生率高达26%-43%,发生机制非常复杂,与血压异常升高、应激性高血糖、高血脂、动脉粥样硬化、脑水肿、C反应蛋白、身体抵抗力低下有关。溶栓治疗者应在溶栓24小时排除HT后开始使用抗血小板药物阿司匹林或氯吡格雷。阿司匹林是治疗进展性脑梗死的常用药,其能够有效抑制血小板的粘附、聚集和释放,预防血栓进一步扩大和新的血栓形成,但对神经功能难以发挥保护作用,丁苯酞对进展性脑梗死有较好的恢复脑灌注和脑保护作用,丁苯酞联合抗血小板治疗进展性脑梗死能有效改善神经功能^[22-24]。在本研究中,有2例出现卒中后抑郁,予SSRIs类药物氟西汀治疗。卒中后抑郁是指临床表现为抑郁心境且与卒中中事件相关的情感障碍性疾病,与5-羟色胺和去甲肾上腺素的平衡失调有关^[25]。有研究表明,SSRIs不仅可改善情绪,并可能有促进神经再生等作用^[26,27]。阿替普酶通过调节BDNF生物合成和快速溶解血栓提高了因缺血而受损神经元的存活使卒中后抑郁的发病率降低^[28,29]。

综上所述,处于静脉溶栓时间窗内的急性脑梗死患者应优先考虑采用静脉溶栓治疗,可显著改善神经功能和远期预后。小剂量阿替普酶(0.6 mg/kg)与标准剂量阿替普酶(0.9 mg/kg)的有效性相当,而小剂量可用于体重在83.3kg以内的患者,为减轻患者经济负担,可考虑选择小剂量。小剂量阿替普酶出血风险低于标准剂量,高龄患者可选用小剂量以降低出血风险和病死率。脑梗死治疗包括药物治疗、肢体康复、语言训练、心理康复、健康教育等^[30],根据患者情况开展个体化治疗,为避免复发风险,卒中后应尽早开始二级预防。

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