

D-二聚体水平对急性脑梗死患者溶栓疗效的预测意义^{*}

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摘要 目的:探讨 D-二聚体水平对急性脑梗死(ACI)患者静脉溶栓疗效的预测作用。方法:选取 100 例患 ACI 并接受阿替普酶静脉溶栓治疗的患者,采用 Sysmex Cs-5100 全自动检测仪分别检测其溶栓前、后 24 h 内 D-二聚体水平,同时记录患者美国国立卫生院卒中量表评分(NIHSS),并进行相关性分析。结果:病情好转患者 70 例,为好转组,恶化患者 30 例,为恶化组。2 组到达医院至开始静脉溶栓时间(DNT)、性别和入院时 NIHSS 评分比较,差异有统计学意义(均 $P < 0.05$)。所有患者溶栓前、后 24 h 凝血酶原时间(PT)、国际标准化比值(INR)、活化部分凝血酶原时间(APTT)、凝血酶时间(TT)和 D-二聚体水平比较,差异均有统计学意义(均 $P < 0.05$);且恶化组 D-二聚体水平均显著高于好转组(均 $P < 0.05$)。Logistic 回归分析示,溶栓后 24 h D-二聚体水平显著升高是患者溶栓后病情恶化的危险因素。溶栓后 NIHSS 评分与溶栓前、后 24 h 血浆 D-二聚体水平分别存在明显正相关性(r 分别为 0.316、0.451,均 $P < 0.01$)。结论:ACI 患者溶栓后 24 h 内 D-二聚体水平显著升高预示病情恶化。

关键词 D-二聚体;急性脑梗死;静脉溶栓;疗效

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Predictive significance of D-dimer levels in acute cerebral infarction patients receiving thrombolytic therapy JIANG Chen-xiao, YANG Ting, Xi You-li, YAN Si-min, XU Hang, Zhang Qiu-ling, WANG Jun, GE Wei-Hong^{*} Nanjing Drum Tower Hospital Affiliated to Medical College of Nanjing University, Nanjing 210000, China

Abstract Objective: To explore the relationship between the levels of D-dimer and the efficacy of intravenous thrombolysis in patients with acute cerebral infarction. Methods: 100 cases of acute cerebral infarction receiving thrombolytic therapy were selected. Plasma D-dimer levels were measured by Sysmex Cs-5100 automatic detector before intravenous thrombolysis and within 24 h after thrombolysis, respectively, to evaluate whether they were related to the changes of neurological function recorded as NIHSS score. Results: DNT, sex and NIHSS at admission had significant differences in the improvement group compared with the deteriorating group ($P < 0.05$). PT, INR, APTT, TT and D-dimer levels in 100 patients before and within 24 h after thrombolysis had statistically significant differences ($P < 0.01$ or $P < 0.05$). The levels of D-dimer in the deteriorating group (30 cases) were significantly higher than those in the improvement group (70 cases), both before and within 24 h after thrombolysis ($P < 0.05$). Multivariate logistic regression analysis indicated that the significant increase of D-dimer levels within 24 h after thrombolysis was the risk factor for poor prognosis of acute cerebral infarction patients with thrombolysis. There was a significantly positive correlation between NIHSS score and plasma D-dimer levels before and within 24 h after thrombolysis in patients with acute cerebral infarction ($r = 0.316$ and 0.451 , $P < 0.01$ and $P < 0.001$, respectively). Conclusion: The D-dimer levels within 24 h could be used as a predication indicator for the efficacy of intravenous thrombolysis.

Key words D-dimer; Acute cerebral infarction; Thrombolytic therapy; Prognosis

静脉溶栓是治疗急性脑梗死(acute cerebral infarction, ACI)的措施之一,可激活体内的纤溶系统,诱导凝血和纤溶标志物(如纤维蛋白降解产物、凝血酶原片段 1 + 2 等)大量持续生成^[1],从而改善神

经功能。D-二聚体是一种可溶性纤维蛋白降解产物,可以作为凝血和纤溶激活的标志物,在多种血栓性疾病的诊断和预后判断中有重要的意义^[2~5]。本文分析 100 例 ACI 患者溶栓前、后的凝血指标变化,探讨 D-二聚体水平与 ACI 静脉溶栓疗效的关系,报道如下。

资料与方法

一般资料 选取 2016 年 11 月 ~ 2018 年 9 月

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江苏省南京大学医学院附属鼓楼医院收治的发病 6 h 以内、使用阿替普酶 (Alteplase, rt-PA) 静脉溶栓的 ACI 患者 100 例 (男 62, 女 38), 年龄 34 ~ 87 岁, 平均 (67.5 ± 10.9) 岁。患者入院时美国国立卫生院卒中量表评分 (National Institutes of Health Stroke Scale, NIHSS) (7.9 ± 8.0) 分, 患者到达急诊至开始静脉溶栓的时间 (door to needle time, DNT) 为 (55.8 ± 20.5) min, 使用 rt-PA 平均剂量为 (60.3 ± 11.9) mg。

纳入与排除标准 纳入标准: ①符合《中国急性缺血性脑卒中诊治指南 2018》的诊断标准^[6], 发病 4.5 ~ 6 h 以内、头颅 CT 排除颅内出血; ②既往无出血病史。排除标准: 不符合《中国急性缺血性脑卒中静脉溶栓指南 2016》静脉溶栓条件的患者。本研究患者及其家属均知情并签署同意书。

方法 100 例病例均给予 rt-PA 0.9 mg/kg 静脉治疗, 初始 1 min 内静脉推注 10% rt-PA, 接着 1 h 内静脉滴注 90% rt-PA。采用 NIHSS 评分量表分别评估患者入院时和溶栓后 7 d 的神经功能缺损情况, 定义 Δ = 溶栓后 7d NIHSS 评分 - 溶栓前 NIHSS 评分。根据 Δ 值将 100 例患者分成 2 组, $\Delta \geq 0$ 且住院 7 d 内未发生任何出血情况 (如脑出血、消化道出血、牙龈出血等) 为好转组; 否则或自动出院为恶化组。

2 组患者分别于溶栓前、后 24 h 内抽取 3 mL 静脉血, 置于枸橼酸钠抗凝试管内, 3 500 r/min 离心 10 min, 收集血浆, 采用 Sysmex Cs-5100 全自动检测仪检测凝血酶原时间 (prothrombin time, PT)、国际标准化比值 (international normalized ratio, INR)、活化部分凝血酶原时间 (activated partial thromboplastin time, APTT)、凝血酶时间 (thrombin time, TT), 采用

免疫比浊法检测 D-二聚体水平。

统计学处理 采用 SPSS 24.0 统计学软件, 计量资料以 ($\bar{x} \pm s$) 表示, 采用 t 检验; 计数资料以百分数 (%) 表示, 采用 χ^2 检验。以 $P < 0.05$ 为差异有统计学意义。

结果

好转组患者 70 例。恶化组患者 30 例, 其中溶栓后脑出血 10 例, 4 例溶栓期间出血, 1 例溶栓期间胃肠道出血, 1 例皮肤淤斑, 8 例死亡, 1 例自动出院以及 5 例病情加重 (无出血)。

好转组 DNT 明显短于恶化组 ($P < 0.05$)。恶化组患者入院时 NIHSS 评分高于好转组 ($P < 0.01$), 提示入院时卒中症状较轻的患者经过静脉溶栓之后能达到较好的疗效。好转组中男性比例明显高于恶化组 ($P < 0.05$), 见表 1。

凝血指标 溶栓后 24 h 内的 PT、INR、APTT 和 D-二聚体水平都明显高于溶栓前 (均 $P < 0.01$); TT 水平较溶栓前也显著升高 ($P < 0.05$), 见表 2。溶栓前、后 24 h 好转组的 D-二聚体水平显著低于恶化组 (均 $P < 0.01$), 见表 3。

Spearman 秩相关分析显示, 溶栓后 7 d 患者 NIHSS 评分与溶栓前和溶栓后 24 h D-二聚体水平均呈正相关 (r 分别为 0.316、0.451, 均 $P < 0.01$)。

ACI 患者静脉溶栓预后的多变量 logistic 回归分析 将 DNT、男性、入院时 NIHSS 评分、溶栓前、后 D-二聚体水平作为自变量, 将 ACI 静脉溶栓的预后作为因变量, 行多变量 logistic 回归分析, 溶栓后 24 h 内 D-二聚体水平是影响预后的危险因素, 见表 4。

表 1 临床基本信息

组别	例	年龄 (岁)	男 [例 (%)]	时间窗 (min)	DNT (min)	rt-PA 使用 剂量 (mg)	体重 (kg)	饮酒史 [例 (%)]	高血压 [例 (%)]
好转组	70	64.8 ± 11.1	48 (68.6) *	175.1 ± 71.8	52.8 ± 22.3 *	61.4 ± 11.4	68.2 ± 12.8	11 (15.7)	44 (62.9)
恶化组	30	73.0 ± 7.9	14 (46.7)	179.4 ± 66.8	62.3 ± 42.9	57.8 ± 12.7	64.2 ± 14.1	1 (3.3)	21 (70.0)
组别	例	高血脂 [例 (%)]	糖尿病 [例 (%)]	房颤 [例 (%)]	冠心病史 [例 (%)]	外周血管 疾病史 [例 (%)]	TIA/卒中史 [例 (%)]	肝肾功能 不全史 [例 (%)]	入院时 NIHSS 评分 (分)
好转组	70	20 (28.6)	25 (35.7)	11 (15.7)	4 (5.7)	5 (7.1)	9 (12.9)	6 (8.6)	6.2 ± 6.5 **
恶化组	30	9 (30.0)	9 (30.0)	9 (30.0)	2 (6.7)	1 (3.3)	1 (3.3)	3 (10.0)	11.9 ± 9.7

注: 与恶化组比较, * $P < 0.05$, ** $P < 0.01$; TIA 指短暂性脑缺血发作

表 2 溶栓前与溶栓后 24 h 内凝血指标水平

时间	例	PT (s)	INR	APTT (s)	TT (s)	D-二聚体 (mg/L)
溶栓前	100	11.2 ± 1.0	1.0 ± 0.1	25.6 ± 3.6	18.9 ± 1.5	0.7 ± 0.9
溶栓后 24 h 内	100	12.2 ± 1.4 *	1.1 ± 0.1 *	27.9 ± 6.6 *	22.5 ± 14.8 **	4.6 ± 6.9 *

注: 与溶栓前比较, * $P < 0.01$, ** $P < 0.05$

表 3 溶栓前、后凝血指标水平

(x̄ ± s)

组别	例	PT(s)	INR	APTT(s)	TT(s)	D-二聚体(mg/L)
好转组						
溶栓前	70	11.2 ± 1.0	0.98 ± 0.09	26.2 ± 3.8	19.0 ± 1.6	0.52 ± 0.51
溶栓后	70	12.2 ± 1.4	1.06 ± 0.12	28.7 ± 7.4	23.3 ± 17.7	2.46 ± 2.69
恶化组						
溶栓前	30	11.3 ± 1.0	0.99 ± 0.08	24.2 ± 2.8	18.8 ± 1.0	1.17 ± 1.30 *
溶栓后	30	12.2 ± 1.3	1.06 ± 0.11	26.2 ± 4.0	20.6 ± 2.2	9.49 ± 10.44 *

注:与好转组比较,* $P < 0.01$

表 4 静脉溶栓预后的多变量 logistic 回归分析

变量	OR	95% CI	P 值
DNT	1.013	0.995 ~ 1.031	0.172
男性	1.452	0.448 ~ 4.710	0.534
入院时 NIHSS 评分	1.055	0.970 ~ 1.148	0.209
溶栓前 D-二聚体	1.393	0.588 ~ 3.300	0.451
溶栓后 24 h D-二聚体	1.197	1.019 ~ 1.408	0.029

讨论

本研究中 ACI 患者静脉溶栓疗效与 DNT 时间、性别及入院时 NIHSS 评分有关。一项纳入了 NINDS、ECASS I + II 和 ATLANTIS 等 6 项 RCT 研究的荟萃分析显示,ACI 患者越早静脉溶栓(尤其开始溶栓时间 $< 90\text{min}$),患者获益越大、预后越好^[7]。与本研究结论一致。本研究发现缩短 DNT 时间,能够有效改善患者溶栓后的神经功能缺损情况;女性脑卒中患者静脉溶栓后神经功能恢复比男性差^[8,9];入院时 NIHSS 评分越低,患者溶栓后神经功能恢复越好^[10,11]。

本研究中 ACI 患者静脉溶栓治疗后 24 h PT、INR、APTT、TT 和 D-二聚体水平较溶栓前显著升高(均 $P < 0.05$)。原因是静脉溶栓过程使用的 rt-PA 激活了大量凝血标志物,同时激活纤溶酶原转化为纤溶酶,进一步诱导纤维蛋白降解,导致 D-二聚体水平显著性升高。也有报道认为,患者体内血栓对内源性纤溶系统溶栓过程存在高抗性^[12],因此 D-二聚体呈现高水平状态。

研究发现,D-二聚体值和脑梗死严重程度具有线性相关,可用于判断 ACI 患者的预后^[13,14]。Hsu 等^[15]也发现高水平 D-二聚体能够预测 ACI 患者接受 rt-PA 静脉溶栓之后的不良预后,入院时 D-二聚体值与 ACI 溶栓后脑出血发生具有独立相关性,可能因为高水平 D-二聚体激活炎症反应、诱导血肿扩大^[15,16]。本研究中 ACI 患者静脉溶栓后 NIHSS 评分与溶栓前、后 24 h 血浆 D-二聚体水平均存在明显正相

关性(均 $P < 0.01$),提示患者 D-二聚体水平越高、神经功能缺损越严重,这与相关研究结论一致^[17]。多变量 logistic 回归分析表明,溶栓后 24 h D-二聚体水平显著升高是 ACI 溶栓后不良事件的危险因素。

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