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单抗联合抗凝治疗不同亚型进展性分支动脉粥样硬化病的临床效果

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[摘要] 目的: 比较拜阿司匹林联合依诺肝素钠治疗不同亚型进展性分支动脉粥样硬化病(branch atheromatous disease, BAD)的临床疗效。方法: 选取104例入院1周内出现脑卒中进展的BAD患者, 按梗死灶部位不同分为两组: 脑桥旁正中动脉(pontine paramedian artery, PPA) BAD组(PPA-BAD组)($n=58$)和豆纹动脉(lenticulostriate artery, LSA) BAD组(LSA-BAD组)($n=46$)。两组患者治疗方案相同: 入院后予拜阿司匹林联合氯吡格雷抗血小板治疗, 治疗期间出现病情进展则换用拜阿司匹林联合依诺肝素钠治疗, 其他常规辅助治疗脑梗死的药物相同。记录两组患者卒中进展时和出院时的美国国立卫生研究院卒中量表(NIH Stroke Scale, NIHSS)评分、Barthel指数(Barthel index, BI)评分、血浆纤维蛋白原(fibrinogen, FIB)和CRP浓度, 比较两组临床疗效。结果: 出院时, 两组NIHSS评分均减少、BI评分均增加, FIB浓度和CRP浓度明显降低, 与病情进展时比较差异均有统计学意义($P<0.05$)。PPA-BAD组出院时与病情进展时的NIHSS评分差值以及BI评分差值均显著高于LSA-BAD组($P<0.05$); 两组出院时与病情进展时的FIB浓度差值和CRP浓度差值的差异均无统计学意义($P>0.05$)。结论: 早期抗血小板联合抗凝治疗PPA-BAD的临床疗效优于LSA-BAD。

[关键词] 分支动脉粥样硬化病; 进展性卒中; 桥脑旁正中动脉; 豆纹动脉; 抗凝治疗

Efficacy of an antiplatelet combined anticoagulation therapy on progressive branch atheromatous disease in different subtypes

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Abstract **Objective:** To compare the clinical efficacy of aspirin combined with enoxaparin in the treatment of different subtypes of progressive branch atheromatous disease (BAD). **Methods:** According to the different of infarct site, 104 consecutive BAD patients with progressive stroke within 1-week admission were classified into two groups: a pontine paramedian artery BAD group (PPA-BAD, $n=58$) and a lenticulostriate artery BAD group (LSA-BAD,

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$n=46$). All patients administrated with the same treatment programs, the anti-platelet therapy with aspirin and clopidogrel was applied after enrollment, while replaced by the aspirin combined with enoxaparin treatment when the patient's condition aggravated, other clinical routines treatment of cerebral infarction were same. The patients NIHSS score and Barthel index (BI) when progression and discharge were assessed respectively. The plasma levels of fibrinogen (FIB) and CRP were measured at the time of progression and discharge and the effect of both treatments was compared. **Results:** There were significant differences in NIHSS score, BI score, FIB concentration and CRP concentration between the two groups at the time of stroke progression and at discharge ($P<0.05$). When both group patients were discharged, The NIHSS scores were reduced and the BI scores were increased, FIB concentration and CRP concentration were significantly decreased. In the PPA-BAD group, the differences of NIHSS score, BI score between progression and discharge were significantly higher than those in the LSA-BAD group ($P<0.05$). However, there was no significant difference in FIB or CRP concentrations difference between discharge and progression of the two groups ($P>0.05$). **Conclusion:** The clinical efficacy of anti-platelet combined with anticoagulation in the early treatment of PPA-BAD is better than that of LSA-BAD.

Keywords branch atheromatous disease; progressive stroke; pontine paramedian artery; lenticulostriate artery; anticoagulant therapy

分支动脉粥样硬化病(branch atheromatous disease, BAD)是颅内小血管病变引起的局部脑组织急性缺血性疾病,临床上常出现病情进展。脑桥旁正中动脉(pontine paramedian artery, PPA)供血区和豆纹动脉(lenticulostriate artery, LSA)供血区是BAD最为常见的病变部位^[1-2]。目前对BAD的发病机制仍认识不足,多数观点认为是穿支动脉开口处的动脉粥样硬化所致,临床治疗效果亦不理想。本文回顾性总结抗血小板联合抗凝治疗PPA-BAD和LSA-BAD的临床疗效,并予以比较。

1 对象与方法

1.1 对象

收集2013年1月至2016年12月廊坊市人民医院收治的104例住院期间出现病情进展的BAD患者的临床资料,男61例,女43例,年龄37~92(61.4 ± 10.8)岁。入组标准:1)PPA-BAD梗死灶位于PPA供血区,头颅DWI显示由脑桥深部延伸至脑桥腹侧表面的梗死灶,基底动脉狭窄率 $<50\%$,无心源性栓子来源;2)LSA-BAD梗死灶位于LSA供血区,在头颅DWI上 ≥ 3 个层面,大脑中动脉、颈内动脉狭窄率 $<50\%$,未见心源性栓子来源;3)脑卒中进展患者入院1周内任一时间与入院时相比,美国国立卫生研究院卒中量表(NIH Stroke Scale, NIHSS)评分增加 ≥ 1 分,或起病6 h后至入院前肢体无力明显加重^[3]。排除标准:1)颅内出血,如硬膜外血肿、蛛网膜下腔出血、颅内血肿;2)实验室检查凝血机制异常,有出血倾向的患者;3)有出血性疾病及感染性疾病者;4)免疫系

统疾病、恶性肿瘤、颅内其他部位新鲜梗死等。所有患者家属签署知情同意书,研究方案经廊坊市人民医院伦理委员会批准。

1.2 方法

按梗死病灶部位不同,将患者分为2组:PPA-BAD组($n=58$)和LSA-BAD组($n=46$)。所有患者入院后均予拜阿司匹林肠溶片(100 mg,口服,1次/d)联合氯吡格雷(75 mg,1次/d,口服)抗血小板治疗,辅以他汀类、依达拉奉、丁苯酞等常规治疗脑梗死的药物。出现病情进展则改用拜阿司匹林肠溶片(100 mg,口服,1次/d)联合依诺肝素钠注射液(0.6 mL,1次/12 h,皮下注射)治疗1周,辅助治疗药物相同。观察指标:患者病情进展时和出院时的NIHSS评分、Barthel指数(Barthel index, BI)评分、血浆纤维蛋白原(fibrinogen, FIB)浓度及CRP浓度,比较两组临床疗效。

1.3 统计学处理

研究结果数据用均数 \pm 标准差($\bar{x}\pm s$)表示,应用SPSS 18.0软件进行统计分析,组间均数比较采用独立样本 t 检验。检验水准 $\alpha=0.05$ 。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 出血情况

两组治疗期间均未见出血倾向,加用抗凝前后的凝血机制均未见异常。

2.2 神经功能评分

PPA-BAD组和LSA-BAD组加用抗凝治疗后, NIHSS评分均显著降低, BI评分均显著升高, 差异有统计学意义($P < 0.05$, 表1)。PPA-BAD组的NIHSS评分差值和BI差值均显著高于LSA-BAD组, 差异有统计学意义($P < 0.05$, 图1)。

2.3 生化指标检测

与进展时相比, PPA-BAD组和LSA-BAD组患者出院时血浆CRP浓度和FIB浓度均显著降低, 差异有统计学意义($P < 0.05$, 表2)。两组患者出院时与进展时的CRP和FIB浓度差值比较均无显著差异, 差异无统计学意义($P > 0.05$, 图1)。

表 1 两组神经功能评分 ($\bar{x} \pm s$)

Table 1 Neurological function scores of the two groups ($\bar{x} \pm s$)

分组	NIHSS评分		BI评分	
	进展时	出院时	进展时	出院时
PPA-BAD	15.25 ± 1.38	4.09 ± 0.76*	45.13 ± 4.75	89.71 ± 5.64 [§]
LSA-BAD	14.32 ± 1.43	9.93 ± 1.45*	46.32 ± 3.53	71.97 ± 6.32 [§]

与同组进展时 NIHSS 评分比较, * $P < 0.05$; 与同组进展时 BI 评分比较, [§] $P < 0.05$ 。

Compared with NIHSS score when progress in the same group, * $P < 0.05$; compared with BI score when progress in the same group, [§] $P < 0.05$.

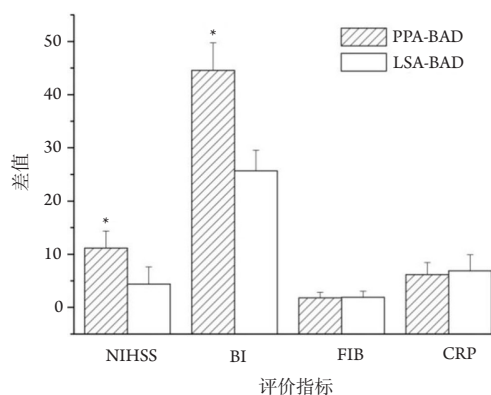


图1 两组抗凝前后的神经功能评分差值及生化指标差值比较

Figure 1 Comparison of differences in neurological function scores and biochemical indexes between the two groups before and after anticoagulation

与LSA-BAD组比较, * $P < 0.05$ 。

Compared with the LSA-BAD group, * $P < 0.05$.

表 2 两组生化检验结果 ($\bar{x} \pm s$)

Table 2 Biochemical test results of the two groups ($\bar{x} \pm s$)

分组	FIB/(g·L ⁻¹)		CRP/(mg·L ⁻¹)	
	进展时	出院时	进展时	出院时
PPA-BAD	4.58 ± 0.97	2.79 ± 1.04*	13.78 ± 4.31	7.62 ± 2.37 [§]
LSA-BAD	4.72 ± 1.10	2.81 ± 0.95*	14.32 ± 3.53	7.45 ± 2.81 [§]

与同组进展时 FIB 浓度比较, * $P < 0.05$; 与同组进展时 CRP 浓度比较, [§] $P < 0.05$ 。

Compared with FIB concentration when progress in the same group, * $P < 0.05$; compared with CRP concentration when progress in the same group, [§] $P < 0.05$.

3 讨论

BAD的临床表现以运动障碍为主, 病程早期容易出现卒中进展^[4]。本研究的前期工作^[5]已经证实, 应用阿司匹林联合依诺肝素钠治疗进展性BAD, 可显著改善患者的早期神经功能恶化(early neurological deterioration, END), 提高其生活自理能力, 临床疗效优于阿司匹林和氯吡格雷双联抗血小板治疗。在此基础上, 本研究进一步比较了抗血小板联合抗凝对不同类型BAD出现病情进展时的治疗效果。

依诺肝素为低分子量肝素制剂, 通过抑制凝血因子活性^[6]、促进纤溶、促进内源性氨基多糖释放、改变患者血液黏度、增加血细胞表面电荷等机制, 改善高凝状态、抗血栓、促进血栓溶解和血管再通, 具有改善侧支循环、挽救缺血半暗带、改善神经功能缺损等作用^[7-8]。急性缺血性卒中时应用依诺肝素可降低运动神经元中多巴胺诱导的脑外伤, 同时增加血液灌注, 显著减小脑梗死面积, 从而减轻梗死脑组织缺氧^[9]。有研究^[10]发现: 36.1%豆纹动脉供血区和59.5%脑桥动脉供血区的脑梗死为BAD。在LSA和PPA供血区的BAD患者, 观察到的END明显增多, NIHSS评分明显升高^[4,11], 高NIHSS评分在PPA-BAD和LSA-BAD中都预示预后不良^[12]。本研究结果显示: 两组出院时的NIHSS评分较进展时均显著降低, BI评分均显著升高, 说明在单抗基础上加用依诺肝素钠治疗, 可明显改善进展性BAD患者的神经功能缺损, 提高患者的日常生活活动能力。该结果与前述研究^[5]一致。

CRP是缺血性卒中急性期的主要炎症反应物质, 可作为动脉粥样硬化性脑梗死风险和预后的高敏感指标^[13]。血浆CRP水平与BAD的进展显著相关, 与脑梗死急性期的严重程度和预后呈正相关^[4], 血浆CRP水平升高可独立预测BAD患者病情预后^[14]。FIB是凝血因子之一, 与血栓形成、血小板聚集、血液黏度、动脉粥样硬化斑块形成及炎症有关。急性进展性脑卒中的FIB水平明显增高^[15]。Zang等^[16]研究发现: 观察血浆CRP和FIB的水平变化可能有助于早期识别和及时治疗进展性缺血性卒中。本研究中, 两种亚型的BAD患者在出现病情进展时, 血浆CRP和FIB的水平均明显高于正常, 经单抗联合抗凝治疗后, 两组患者的血浆CRP和FIB水平较进展时均有所降低, 差异显著。提示单抗联合抗凝能抑制BAD卒中进展, 改善患者的END症状, 机制可能与抑制患者的血浆

CRP和FIB浓度升高有关。

对比单抗联合抗凝治疗对两组患者出院时与进展时的评分差值及血浆生化指标差值影响, 结果表明: 一方面单抗联合抗凝治疗对PPA-BAD卒中进展的疗效优于LSA-BAD组, 另一方面单抗联合抗凝治疗对两组患者血浆CRP和FIB浓度的抑制程度无显著差别。提示, 尽管CRP和FIB血浆浓度的降低可能与PPA-BAD和LSA-BAD卒中进展时的神经功能缺损及日常生活活动能力改善有关, 但是CRP和FIB浓度的降低程度并非导致两组疗效有区别的主要因素。

本研究样本量少、治疗效果观察时间较短, 今后应开展大样本、多中心及长随访研究, 以明确远期疗效。此外, 抗凝对PPA-BAD效果好的原因有待后续研究阐明。

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