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依达拉奉联合克林澳对急性脑梗死患者血清 MMP-3、MMP-9、TIMP-1、EPCs 的影响及疗效观察 *

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摘要 目的:研究依达拉奉联合克林澳对急性脑梗死患者血清 MMP-3(基质金属蛋白酶-3)、MMP-9(基质金属蛋白酶-9)、TIMP-1(组织基质金属蛋白酶抑制剂1)、EPCs(内皮祖细胞)的影响及疗效观察。**方法:**选取我院收治的114例急性脑梗死患者,按照随机数表法分为联合治疗组(n=57)和单独治疗组(n=57)。单独治疗组仅应用依达拉奉治疗,联合治疗组则联合克林澳治疗。观察并比较两组患者临床治疗效果、NIHSS(美国国立卫生研究院卒中量表)评分变化情况、实验室指标水平变化情况、血脂水平变化情况以及不良反应发生情况。**结果:**治疗后,联合治疗组基本痊愈和显著进步的患者达到49例,其总有效率为85.96%,而单独治疗组基本痊愈和显著进步的患者仅为39例,其总有效率为68.42%,两组比较差异显著(P<0.05)。治疗14d和28d后,患者的评分均较治疗前有明显下降,同时,联合治疗组下降水平明显优于单独治疗组(P<0.05)。两组患者MMP3和MMP9水平较治疗前显著下降,而TIMP-1和EPCs水平则明显上升,且联合治疗组MMP3和MMP9水平下降情况和TIMP-1和EPCs水平上升情况均明显优于单独治疗组(P<0.05)。治疗14d和28d后,患者血脂各指标水平较前一次测量有明显下降,且单独治疗组较联合治疗组下降更为明显(P<0.05)。联合治疗组不良反应发生率为5.26%;单独治疗组不良反应发生率为10.53%,不良反应发生率比较无统计学意义(P>0.05)。**结论:**依达拉奉联合克林澳应用于治疗急性脑梗死患者疗效确切,有效改善血清MMP-3、MMP-9、TIMP-1、EPCs以及患者血脂异常情况,促进血管新生,保护患者脑组织。

关键词:依达拉奉;克林澳;急性脑梗死;MMP-3;MMP-9;TIMP-1;EPCs

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To Observe the Effect of Edaravone Combined with Cinepazide Maleate on Patients with Acute Cerebral Infarction Serum MMP-3, MMP-9, TIMP-1, EPCs*

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ABSTRACT Objective: To study the effect of edaravone combined with cinepazide maleate on patients with acute cerebral infarction serum MMP-3, MMP-9, TIMP-1, EPCs. **Methods:** 114 cases with acute cerebral infarction were researched, according to the random number table they were divided into combined treatment group(n=57) and the single treatment group(n=57). The single treatment group was only treated with edaravone, and the combined treatment group was treated with edaravone and cinepazide maleate. They were compared with clinical treatment effect, NIHSS score change, laboratory index level change, blood lipid level change and adverse reactions. **Results:** After treatment, combined treatment group cured and significantly improved patients reached 49 cases, the total effective rate was 85.96%, and the single treatment group cured and significant progress in patients with only 39 cases, the total effective rate was 68.42%, there was significant difference between two groups (P<0.05). After the treatment of 14 d and 28 d, the scores of patients were significantly lower than those before treatment, while the level of decrease in the combined treatment group was better than that in the single treatment group (P<0.05). Two groups of patients with MMP3 and MMP9 levels decreased significantly, while TIMP-1 and EPCs levels increased significantly, and the combined treatment group MMP3 and MMP9 decreased and TIMP-1 and EPCs levels were significantly better than the single treatment group (P<0.05). After treatment of 14 d and 28 d, the indexes of blood lipid in patients decreased significantly compared with the previous measurement, and the decrease in the individual treatment group was more obvious than that in the combined treatment group (P<0.05). The adverse reaction rate was 5.26% in the combined treatment group, the adverse reaction rate in the single treatment group was 10.53%, and the adverse reaction rate was not statistically significant(P>0.05). **Conclusion:**

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Edaravone combined with cinepazide maleate used in the treatment of patients with acute cerebral infarction is effective, effectively improve the serum levels of MMP-3, MMP-9, TIMP-1, EPCs and blood lipid abnormalities, promote angiogenesis, protect the brain tissue of patients.

Key words: Edaravone; Cinepazide maleate; Acute cerebral infarction; MMP-3; MMP-9; TIMP-1; EPCs

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前言

急性脑梗死是一种较为常见的脑血管疾病,也是全球致死致残率较高的疾病之一^[1]。该病主要特点有高发病率、复发率、致残率以及死亡率等,随着逐年增长的发病率,为人们的生活和健康带来较大的困扰^[2,3]。国外研究结果显示,由于临床研究上对于该病的发病机制尚无定论,加上临床治疗中该病发病机制较为复杂,因此对于该病的治疗也一直是医学界的一大难题^[4,5]。临床治疗该病主要应用抗凝、降纤、抗血小板、中药、神经保护剂以及手术等治疗,此外,血管扩张剂的应用也越来越广泛,且取得了一定的成效。但近年来有学者提出,多种细胞因子不仅参与急性脑梗死过程中,还涉及相关的病理过程^[6]。其中 MMP 家族与患者梗死后发生继发性脑损伤以及炎症反应关系密切,而 EPCs 细胞则能在病理过程中参与血管的修复和再生,很好维持血管功能^[7,8]。因此,在患者发生脑梗死后对于上述各指标水平变化情况的监测显得尤为重要,不仅能够了解疾病进展情况,还能根据相关情况改善预后。故本文便应用依达拉奉联合

血管扩张剂克林澳对急性脑梗死患者进行治疗,以观察两药联合治疗的临床效果以及治疗后对血清 MMP-3、MMP-9、TIMP-1、EPCs 等有何影响。现将报道如下。

1 材料与方法

1.1 材料

选取 2015 年 4 月至 2017 年 4 月期间于我院接受治疗的 114 例急性脑梗死患者纳入研究,将所有患者按照随机数字表法分为单独治疗组和联合治疗组,每组 57 例患者。纳入标准:(1)符合《中国急性缺血性脑卒中诊治指南 2010》^[9]中关于研究疾病的诊断标准者;(2)临床经颅脑 MRI 或者 CT 确诊为急性脑梗死者;(3)发病时间 ≤ 72 h 者;(4)患者及其家属知情并同意本研究。排除标准:(1)血性脑梗死或者脑出血者;(2)合并严重糖尿病、心脏病者;(3)合并严重痴呆或精神疾病者。整个研究经我院伦理委员会批准后实施。两组患者在年龄差距、性别组成、有无症状等临床资料的比较无显著差异,具有可比性($P>0.05$),见表 1。

表 1 两组患者临床资料比较

Table 1 Comparison of the clinical data of two groups

Groups	n	Age(year)	Gender(M/F)	Past illness(n)	Symptomatic(n)	Asymptomatic(n)	Disease time(d)
Combined treatment group	57	62.3 $\pm$ 5.7	33/24	36(63.16)	28(49.12)	29(50.88)	2.1 $\pm$ 0.5
Single treatment group	57	61.9 $\pm$ 6.1	35/22	38(66.67)	29(50.88)	28(49.12)	2.2 $\pm$ 0.7

1.2 方法

入院后两组患者均给予降血压、颅压,调脂,降糖,维持体液平衡,抗血小板聚集,补充电解质,对症支持治疗等常规治疗。

单独治疗组加用依达拉奉(生产厂商:南京先声东元制药有限公司;生产批号:20141121;规格:20 mL:30 mg)治疗。将 30 mg 依达拉奉注射液加入 100 mL 0.9%生理盐水中混合后进行静脉滴注,每日 2 次。

联合治疗组则联合依达拉奉和克林澳(生产厂商:北京四环制药有限公司;生产批号:20141203;规格:10 mL:0.32 g $\times$ 2 支/盒)治疗。依达拉奉注射液应用与单独治疗组同,另将 320 mg 克林澳注射液加入生理盐水或者 5%葡萄糖液中混合后静脉滴注,每日 1 次。两组患者均连续治疗 28 d。

1.3 观察指标

① 神经功能缺损评分:参照 NIHSS 评分量表标准分别于患者治疗前、治疗 14 d 以及治疗 28 d 进行评分。② 血清各指标水平检测:两组患者均于确诊后以及治疗结束后清晨空腹情况下抽取静脉血 5 mL,离心(时间:15 min,转速:2000 r/min)分离

血清后待检。应用 ELISA 法检测 MMP3、MMP9 以及 TIMP-1 水平,所有操作方法严格按照说明书进行,采用流式细胞仪检测 EPCs 细胞。③ 血脂各指标水平检测:两组患者均于确诊后以及治疗结束后清晨空腹情况下抽取静脉血 5 mL,离心(时间:15 min,转速:2000 r/min)分离血清后检测高、低密度脂蛋白胆固醇(HDL-C、LDL-C)、甘油三酯(TG)以及总胆固醇(TC)。上述试剂盒均购自北京中生北控生物科技股份有限公司。④ 不良反应:观察并记录两组患者治疗过程中出现的不良反应情况。

1.4 疗效评定标准

基本痊愈:NIHSS 评分减少 90%以上,0 级病残程度;显著进步:NIHSS 评分减少 46%以上,1~3 级病残程度;进步:NIHSS 评分减少 18%以上;无变化:NIHSS 评分减少不足 18%。总有效率=基本痊愈率+显著进展率^[10]。

1.5 统计学分析

本次实验数据处理选择 SPSS11.5 软件包进行,患者 NIHSS 评分变化情况采取计量资料采用($\bar{x} \pm s$)来表示,进行 t 检验,计数资料以[n(%)]表示,采用 χ^2 检验进行比较,患者治

疗后临床效果等级资料比较采用秩和检验(Wilcoxon 两样本比较法)进行, $P < 0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者临床治疗效果比较

表 2 两组患者临床治疗效果比较[n(%)]

Table 2 Comparison of clinical treatment effect between two groups[n(%)]

Groups	n	Basic recovery	Significant progress	Progress	Unchanged	Total efficiency (%)
Combined treatment group	57	18	31	8	0	85.96
Single treatment group	57	9	30	17	1	68.42 [▲]

注:与联合治疗组相比, * $P < 0.05$ 。

Note: Compared with combined treatment group, * $P < 0.05$.

2.2 两组患者治疗前后 NIHSS 评分变化情况比较

治疗前, 两组患者的 NIHSS 评分比较无统计学意义($P > 0.05$);但在治疗 14 d 和 28 d 后, 患者的评分均较治疗前有明显

治疗后, 联合治疗组基本痊愈和显著进步的患者达到 49 例, 其总有效率为 85.96%, 而单独治疗组基本痊愈和显著进步的患者仅为 39 例, 其总有效率为 68.42%, 两组比较差异显著($P < 0.05$), 见表 2。

下降, 同时, 联合治疗组下降水平明显优于单独治疗组($P < 0.05$), 见表 3。

表 3 两组患者治疗前后 NIHSS 评分变化情况比较($\bar{x} \pm s$, 分)

Table 3 Comparison of NIHSS scores before and after treatment between two groups($\bar{x} \pm s$, points)

Groups	n	Before treatment	14 days after treatment	28 days after treatment
Combined treatment group	57	21.72 $\pm$ 8.75	11.93 $\pm$ 3.58 [#]	8.91 $\pm$ 3.22 [#]
Single treatment group	57	21.38 $\pm$ 7.69	15.16 $\pm$ 4.59 ^{#*}	13.98 $\pm$ 6.52 ^{#*}

注:与联合治疗组相比, * $P < 0.05$;与治疗前相比, [#] $P < 0.05$ 。

Note: Compared with combined treatment group, * $P < 0.05$; Compared with before treatment, [#] $P < 0.05$.

2.3 两组患者治疗前后实验室指标水平变化情况比较

治疗前, 两组患者 MMP3、TIMP-1、EPCs 以及 MMP9 等实验室指标水平比较无明显差异($P > 0.05$); 治疗后, 两组患者 MMP3 和 MMP9 水平较治疗前显著下降, 而 TIMP-1 和 EPCs

水平则明显上升, 且联合治疗组 MMP3 和 MMP9 水平下降情况和 TIMP-1 和 EPCs 水平上升情况均明显优于单独治疗组($P < 0.05$), 见表 4。

表 4 两组患者治疗前后实验室指标水平变化情况比较($\bar{x} \pm s$)

Table 4 Comparison of the level of laboratory indexes before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	Time	MMP3(μ g/L)	MMP9(ng/mL)	TIMP-1(ng/mL)	EPCs(One /10 million units)
Combined treatment group	57	Before treatment	61.76 $\pm$ 12.67	72.48 $\pm$ 61.98	364.77 $\pm$ 77.89	20.14 $\pm$ 7.22
		14 days after treatment	42.39 $\pm$ 9.26 [#]	38.11 $\pm$ 21.86 [#]	427.97 $\pm$ 99.12 [#]	27.26 $\pm$ 3.14 [#]
Single treatment group	57	Before treatment	60.23 $\pm$ 11.28	77.37 $\pm$ 89.53	376.39 $\pm$ 97.18	20.23 $\pm$ 7.19
		14 days after treatment	51.06 $\pm$ 10.15 ^{#*}	58.45 $\pm$ 23.81 ^{#*}	492.16 $\pm$ 95.63 ^{#*}	35.58 $\pm$ 3.48 ^{#*}

注:与联合治疗组相比, * $P < 0.05$;与治疗前相比, [#] $P < 0.05$ 。

Note: Compared with combined treatment group, * $P < 0.05$; Compared with before treatment, [#] $P < 0.05$.

2.4 两组患者治疗前后血脂水平变化情况比较

治疗前, 两组患者血脂各指标水平比较无统计学意义($P > 0.05$);治疗 14d 和 28d 后, 患者血脂各指标水平均较前一次测量有明显下降, 且单独治疗组较联合治疗组下降更为显著($P < 0.05$), 见表 5。

2.5 安全性评价

治疗后, 联合治疗组发生头昏、失眠 1 例, 皮肤瘙痒 1 例, 心悸 1 例, 其不良反应发生率为 5.26%;单独治疗组发生头昏、

失眠 1 例, 皮肤瘙痒 2 例, 心悸 3 例, 其不良反应发生率为 10.53%, 但两组患者在治疗结束后均逐渐消失, 其不良反应发生率比较无统计学意义($\chi^2 = 1.0857, P > 0.05$)。

3 讨论

急性脑梗死(Acute cerebral infarct, ACI)主要指突然的脑供血中断而引发的脑组织坏死, 其病灶主要由围绕病灶的缺血半暗带和中心坏死区所组成, 一般中心坏死区细胞完全死亡而

不可逆,但缺血半暗带却有可能恢复,因此急性脑梗死的治疗重点是通过积极及时有效的救治恢复受损细胞^[11,12]。但是对于大部分血红蛋白、红细胞增加,血液粘稠度高的患者,应用单药

治疗的效果不尽如人意。故本研究在临床上应用依达拉奉和克林澳两药联合对急性脑梗死患者进行治疗,以比较联合治疗和单独治疗的临床疗效。

表 5 两组患者治疗前后血脂水平变化情况比较($\bar{x} \pm s$, mmol/L)

Table 5 Comparison of changes of blood lipid levels before and after treatment between two groups($\bar{x} \pm s$, mmol/L)

Groups	n	Time	TC	TG	LDL-C	HDL-C
Combined treatment group	57	Before treatment	5.71± 1.21	2.26± 0.33	3.91± 0.55	1.02± 0.19
		14 days after treatment	5.11± 1.24 [#]	1.81± 0.28 [#]	3.06± 0.47 [#]	1.19± 0.26 [#]
		28 days after treatment	4.67± 1.20 [#]	1.51± 0.13 [#]	2.88± 0.38 [#]	1.36± 0.14 [#]
Single treatment group	57	Before treatment	5.58± 1.26	2.23± 0.34	3.97± 0.34	1.03± 0.18
		14 days after treatment	5.44± 1.43 ^{**}	2.16± 0.44 ^{**}	3.83± 0.41 ^{**}	1.09± 0.22 ^{**}
		28 days after treatment	4.46± 1.20 ^{**}	1.12± 0.32 ^{**}	2.52± 0.30 ^{**}	1.16± 0.18 ^{**}

注:与联合治疗组相比, *P<0.05;与治疗前相比, [#]P<0.05。

Note: Compared with combined treatment group, *P<0.05; Compared with before treatment, [#]P<0.05.

依达拉奉作为一种新型的自由基清除剂,其主要作用是能够很好的抑制脑梗死后的脑水肿,减少脑梗死面积,避免脑组织再次损伤^[13]。等研究结果发现,依达拉奉可以有效清除患者体内氧自由基,增加神经组织供氧,对于血红蛋白、红细胞增加,血液粘稠度高患者疗效确切。克林澳是一种新型的内源性腺苷增效剂,不仅具有弱钙拮抗作用,还能促进细胞营养代谢和扩张血管。其用于治疗急性脑梗死的作用主要体现在能很好的扩张脑血管,增加血流量;加强腺苷生理作用,延长扩张血管时间;改善能量代谢和细胞营养,保护细胞功能;抑制血小板聚集,降低血液黏度,避免血栓形成^[14]。本研究中,将上述两种药物联合治疗,发现其临床治疗效果明显优于单独应用依达拉奉治疗的患者,且不良反应发生率也更少,这可能与克林澳用于治疗急性脑梗死所起到的作用有一定关系。

近年来,随着对急性脑梗死疾病的不断深入研究,有学者提出多种细胞因子不仅参与急性脑梗死过程中,还涉及相关的病理过程的观点,其中基质金属蛋白酶(MMPs)是被提及最多的^[15]。MMPs是一组 Zn^{2+} 依赖性蛋白酶,主要存在于细胞外基质中,MMP3 和 MMP9 均为 MMPs 家族成员,两者在患者梗死过程中均出现异常高表达^[16,17]。本研究中,通过对上述指标水平的监测,确实也发现在梗死发生后,其水平出现异常升高,考虑原因可能为脑梗死引发内皮细胞的凋亡和坏死,细胞间信息传递和结构遭到阻碍,从而破坏血脑屏障,导致细胞因子发生联反应。而在治疗后两者水平均又显著下降,说明联合药物治疗可有效控制血脑屏障遭到破坏,使细胞因子不会出现联反应。同时,有研究表明,MMP9 水平与患者脑水肿程度、梗死面积等关系密切^[18]。TIMP-1 则是 MMP9 的内源性抑制剂,两者相互制约又相互依赖,当两者结合时,可有效发挥蛋白水解酶活性^[19]。本研究结果显示,脑梗死患者 TIMP-1 水平治疗后出现显著上升,可能与患者神经细胞自我修复有关。此外,除上述指标能够很好反应脑梗死面积和水肿程度外,EPCs 细胞也能很好的为脑梗死的治疗、预防和预后提供一定的参考价值。EPCs 细胞不仅参与血管内皮的再生和修复,还能有效反应脑血管疾病危险因素,有研究显示,血管疾病危险因素可引发 EPCs 细胞的减

少,加速其衰老,缩短其存活时间^[20]。本研究中,通过监测其水平也发现,脑梗死患者 EPCs 细胞确实显著减少,在治疗后出现明显增多。另外,联合用药治疗后,患者血脂异常情况得到较大改善。

综上所述,依达拉奉联合克林澳应用于治疗急性脑梗死患者疗效确切,不良反应少,可有效改善血清 MMP-3、MMP-9、TIMP-1、EPCs 以及患者血脂异常情况,促进血管新生,保护患者脑组织。

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