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吡拉西坦联合鼠神经生长因子对急性缺血性脑卒中患者的疗效及 Hcy、PCT 和皮质醇水平的影响 *

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摘要 目的：探讨吡拉西坦联合鼠神经生长因子对急性缺血性脑卒中患者的疗效及对同型半胱氨酸（Hcy）、降钙素原（PCT）和皮质醇水平的影响。**方法：**回顾性分析我院 2017 年 2 月～2018 年 11 月收治的 73 例急性缺血性脑卒中患者为研究对象，依据入院先后顺序分为对照组（n=35）和观察组（n=38）。对照组患者采用吡拉西坦治疗，观察组基于对照组加以鼠神经生长因子治疗。观察并比较两组临床疗效，治疗前后美国国立卫生研究院卒中量表（NIHSS）、日常生活能力（ADL），治疗前及治疗 2 周结束时用全自动生化分析仪测定血浆 Hcy 水平，用放射免疫学分析法测定 PCT 水平，用化学发光法测定皮质醇水平，用超声多普勒诊断仪测定基底动脉、左右大脑中动脉血流。**结果：**治疗后，观察组 NIHSS 评分低于对照组（8.96± 1.21）vs（11.27± 1.59）分，ADL 评分高于对照组（74.21± 9.75）vs（66. 04± 8.03）分（*P*<0.05）。观察组总有效率高于对照组 89.47% vs 68.57%（*P*<0.05）。治疗后，观察组 Hcy、PCT 及皮质醇水平低于对照组（14.27± 2.01）vs（18.51± 2.84）μmol/L、（0.25± 0.03）vs（0.31± 0.04）μg/L、（171.93± 23.86）vs（228.75± 30.27）nmol/L（*P*<0.05）。治疗后，观察组脑血流学指标高于对照组基底动脉（43.81± 6.84）vs（39.62± 5.27）mL/min、左大脑中动脉血流（64.27± 9.95）vs（57.03± 7.52）mL/min、右大脑中动脉血流（62.85± 9.01）vs（56.64± 7.42）mL/min（*P*<0.05）。**结论：**吡拉西坦联合鼠神经生长因子能够提高急性缺血性脑卒中的疗效，降低 Hcy、PCT 及皮质醇水平，促进神经功能的恢复。

关键词：急性缺血性脑卒中；吡拉西坦；鼠神经生长因子；同型半胱氨酸；降钙素原；皮质醇

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Efficacy of Piracetam Plus Rat Nerve Growth Factor on Patients with Acute Ischemic Stroke and Its Effects on Hcy, PCT and Cortisol Levels*

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ABSTRACT Objective: To investigate efficacy of piracetam combined with rat nerve growth factor on patients with acute ischemic stroke and its effect on homocysteine (Hcy), procalcitonin (PCT) and cortisol levels. **Methods:** 73 patients with acute ischemic stroke admitted to our hospital from February 2017 to November 2018 were analyzed retrospectively. They were divided into the control group (n=35) and the observation group (n=38) according to the order of admission. Patients in the control group were treated with piracetam, while patients in the observation group were treated with rat nerve growth factor based on the control group. The clinical efficiency, national institutes of health stroke scale (NIHSS), activity of daily living (ADL), before treatment and at the end of 2 weeks of treatment, plasma Hcy level was measured with automatic biochemical analyzer, PCT level was measured with radioimmunoassay, cortisol level was measured with chemiluminescence method, and blood flow of basilar artery and left and right middle cerebral arteries was measured with ultrasonic Doppler diagnostic instrument. **Results:** The total effective rate of the observation group was higher than that of the control group 89.47% vs 68.57%, the difference was statistically significant (*P*<0.05). After treatment, the NIHSS score of the observation group was lower than that of the control group (8.96± 1.21) vs (11.27± 1.59)points, and the ADL score was higher than that of the control group (74.21± 9.75) vs (66.04± 8.03)points, the difference was statistically significant (*P*<0.05). After treatment, the levels of Hcy, PCT and cortisol in the observation group were lower than those in the control group (14.27± 2.01) vs (18.51± 2.84) μmoL/L, (0.25± 0.03) vs (0.31± 0.04) μg/L, (171.93± 23.86) vs (228.75± 30.27) nmoL/L, the difference was statistically significant (*P*<0.05). After treatment, the cerebral blood flow indexes in the observation group were higher than those in the control group (43.81± 6.84) vs (39.62± 5.27) mL/min, left middle cerebral artery blood flow (64.27± 9.95) vs (57.03± 7.52) mL/min, right middle cerebral artery blood flow (62.85± 9.01) vs (56.64± 7.42) mL/min, the difference was statistically significant (*P*<0.05). **Conclusion:** Piracetam plus rat nerve

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growth factor can improve the curative effect of acute ischemic stroke, reduce the levels of Hcy, PCT, cortisol, and promote the recovery of nerve function.

Key words: Acute ischemic stroke; Piracetam; Rat nerve growth factor; Homocysteine; Procalcitonin; Cortisol
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前言

急性缺血性脑卒中是明显危及患者生命安全的疾病，具有高发生率、高致残率及高致死率，大部分患者可遗留程度不一的神经功能症状[1,2]。尽可能的抑制脑缺血后细胞凋亡，能够减轻急性缺血性脑卒中患者的神经功能障碍[3,4]。药物是此类患者的重要治疗手段，其中吡拉西坦是脑代谢的调节药物，能够改善脑循环，保护脑功能，但有研究发现[5]，急性缺血性脑卒中患者单用吡拉西坦的个体疗效差异较大，对部分患者的疗效欠佳。鼠神经生长因子为神经细胞生长的调节因子，可利于神经细胞的生长、修复及再生，减轻周围神经受损程度，近年研究报道其在脑血管疾病中有一定的作用[6,7]。但目前临床缺乏二者联合应用在急性缺血性脑卒中的系统对照研究，相关作用机制也有待进一步探讨。相关研究报道[8]，同型半胱氨酸（Homocysteine, Hcy）参与动脉粥样硬化形成，和脑血管疾病的严重程度及预后有良好相关性。另外缺血性病灶能够影响降钙素原（Procalcitonin, PCT）和皮质醇等表达，从而参与脑组织的再损伤反应，影响神经功能[9]。本研究主要探讨吡拉西坦联合鼠神经生长因子对急性缺血性脑卒中的疗效及对 Hcy、PCT 和皮质醇水平的影响，为二者联合应用提供理论依据。

1 资料与方法

1.1 一般资料

73 例患者依据入院先后顺序分为对照组（n=35）和观察组（n=38），两组基线资料无统计学差异（P>0.05），见表 1。

表 1 两组基线资料分析

Table 1 Analysis of baseline data in two groups

Groups	n	Gender		Age	Location of onset				Complication			Time from onset to admission(h)
		Men and	Women		Basal ganglia infarction	Cerebral lobe infarction	Cerebral-infarction of thalamus	Coronary heart disease	Hypertension	Hyperlipidemia	Diabetes	
The control group	35	20	15	60.19±6.73	18 (51.43)	12 (34.28)	5(14.29)	13 (37.14)	18 (51.43)	11 (31.43)	8(22.86)	7.13±0.82
The observation group	38	18	20	58.91±6.99	21 (55.26)	10 (26.32)	7(18.42)	11 (28.95)	21 (55.26)	13 (34.21)	10 (26.32)	7.31±0.73

1.2 纳入排除标准

73 例入选患者均符合急性缺血性脑卒中诊断标准[10]：① 急性发病；② 脑部 MRI 或 CT 排除脑出血；③ 体征或者症状持续时间不限；④ 局部病灶神经功能损伤，少数患者出现全面神经功能损伤；⑤ 排除非血管性脑部病变；⑥ 凝血功能正常；⑦ 46~71 岁。

排除标准：① 肝肾等功能严重异常；② 既往脑卒中病史；③ 有出血倾向；④ 近期并发严重感染、外伤；⑤ 严重意识障碍；⑥ 自身免疫性疾病；⑦ 恶性肿瘤。

1.3 方法

两组患者入院后均依据《中国急性缺血性脑卒中诊治指南》[10]进行相关基础治疗，发病在 3～6 h 内者予以溶栓治疗。对照组在此基础上联合吡拉西坦（厂家：上海现代哈森(商丘)药业有限公司，规格：5 mL:1 g/ 支，批号：20160811）治疗，静脉注射 6 g 吡拉西坦，每天 2 次，持续治疗 2 周。观察组基于对照组加以鼠神经生长因子（厂家：舒泰神(北京)生物制药股份有限公司，规格：30 μg/ 瓶，批号：20161004）治疗，于臀大肌注射 18 μg 鼠神经生长因子，每天 1 次，持续治疗 4 周。

1.4 观察指标

① 临床疗效评价[10]：于治疗 2 周结束时进行，病残程度为 0 级，美国国立卫生研究院卒中量表（National Institutes of Health Stroke Scale, NIHSS）评分降低≥ 90%为基本痊愈；病残程度为 1～3 级，NISSS 评分下降在 46%～90%为显著进步；NIHSS 评分下降为 18%～45%为进步；NIHSS 降低≤ 17%为无变化，NIHSS 无改变或增加为恶化。基本痊愈、显著进步及进步均判定为总有效；② 临床评分：NIHSS[11]：于治疗前、治疗 2 周结束时进行，分数越低说明神经功能越好。日常生活能力（Activity of Daily Living, ADL）评分[12]：于治疗前、治疗 4 周结束时进行，分数越高说明日常生活能力越高；③ 血液指标：于治疗前、治疗 2 周结束时用全自动生化分析仪（型号：XL600，厂家：贝克曼库尔特商贸（中国）有限公司）测定血浆 Hcy 水平，用放射免疫学分析法测定 PCT 水平，试剂盒来自武汉明德生物科技股份有限公司；用化学发光法测定皮质醇水平，试剂盒来自杭州昊鑫生物科技股份有限公司；④ 脑血流学测定：于治疗前及治疗 2 周结束时采用超声多普勒诊断仪（型号：SSC-400，厂家：上海阿洛卡医用仪器有限公司）测定基底动脉、左右大脑中动脉血流。

1.5 统计学方法

数据处理选用 SPSS18.0 软件包，计量资料用（$\bar{x}\pm s$）表示，

选用 t 检验，计数资料用[例(%)]表示，用 x^2 检验比较，P<0.05 表示差异有统计学意义。

2 结果

2.1 两组疗效分析

观察组总有效率较对照组高，差异有统计学意义(P<0.05)，见表 2。

表 2 两组疗效分析[n(%)]

Table 2 Analysis of curative effect of two groups[n(%)]

Groups	n	Basic recovery	Significant Progress	Progress	No Change	Deterioration	Total efficiency
The control group	35	5(14.29)	8(22.86)	11(31.43)	8(22.85)	3(8.57)	24(68.57)
The observation group	38	9(23.68)	15(39.47)	10(26.32)	3(7.89)	1(2.63)	34(89.47)[b]

Note: [b]Compared with the control group, P<0.05.

2.2 两组 NIHSS、ADL 评分分析

治疗前，两组 NIHSS、ADL 评分比较无统计学意义(P>0.05)；治疗后，两组 NIHSS 均较治疗前下降，ADL 评分相应上升，但观察组 NIHSS、ADL 评分变化更明显，差异有统计学意义(P<0.05)，见表 3。

表 3 两组 NIHSS、ADL 评分分析[n，$\bar{x}\pm s$]

Table 3 Analysis of NIHSS and ADL scores in two groups[n, $\bar{x}\pm s$]

Groups	n	Time	NIHSS(points)	ADL(points)
The control group	35	Before treatment	23.71± 3.81	37.83± 4.82
		After treatment	11.27± 1.59[a]	66.04± 8.03[a]
The observation group	38	Before treatment	24.63± 3.15	39.01± 4.04
		After treatment	8.96± 1.21[ab]	74.21± 9.75[ab]

Note: [a]Compared with before treatment, P<0.05; [b]Compared with the control group, P<0.05.

2.3 两组 Hcy、PCT 及皮质醇分析

治疗前，两组 Hcy、PCT 比较无统计学意义(P>0.05)；治疗后，两组 Hcy、PCT 和皮质醇均较治疗前下降，且观察组 Hcy、PCT 及皮质醇低于对照组，差异有统计学意义(P<0.05)，见表 4。

表 4 两组 Hcy、PCT 及皮质醇分析[n，$\bar{x}\pm s$]

Table 4 Analysis of Hcy, PCT and Cortisol in two groups[n, $\bar{x}\pm s$]

Groups	n	Time	Hcy(μmol/L)	PCT(μg/L)	Cortisol(nmol/L)
The control group	35	Before treatment	26.86± 3.71	0.55± 0.06	351.72± 43.88
		After treatment	18.51± 2.84[a]	0.31± 0.04[a]	228.75± 30.27[a]
The observation group	38	Before treatment	27.53± 3.53	0.56± 0.05	358.04± 41.04
		After treatment	14.27± 2.01[ab]	0.25± 0.03[ab]	171.93± 23.86[ab]

Note: [a]Compared with before treatment, P<0.05; [b]Compared with the control group, P<0.05.

2.4 两组脑血流学指标分析

治疗前，两组脑血流指标比较无统计学意义(P>0.05)；治疗后，两组脑血流指标均较治疗前上升，且观察组脑血流学指标高于对照组，差异有统计学意义(P<0.05)，见表 5。

表 5 两组脑血流学指标分析[mL/min，$\bar{x}\pm s$]

Table 5 Analysis of cerebral blood flow indexes in two groups[mL/min, $\bar{x}\pm s$]

Groups	n	Time	Basilar artery	Middle cerebral artery(left)	Middle cerebral artery (right)
The control group	35	Before treatment	31.08± 4.12	46.81± 6.83	47.33± 5.21
		After treatment	39.62± 5.27[a]	57.03± 7.52[a]	56.64± 7.42[a]
The observation group	38	Before treatment	32.55± 3.65	47.69± 6.04	46.74± 5.80
		After treatment	43.81± 6.84[ab]	64.27± 9.95[ab]	62.85± 9.01[ab]

Note: [a]Compared with before treatment, P<0.05; [b]Compared with the control group, P<0.05.

3 讨论

调查研究报道[13],急性缺血性脑卒中近年来的发生率呈显著上升趋势,其病情危重且变化快,预后不理想。临床研究报道[14],急性缺血性脑卒中梗死病灶在缺血缺氧状态下容易发生代谢性酸中毒,刺激自由基大量生成,导致神经细胞凋亡,引起脑器官功能损伤。相关研究表明[15],尽早应用神经保护和营养神经药物对急性缺血性脑卒中患者预后改善有重要作用,能够有效降低后遗症发生率。

吡拉西坦为氨基丁酸衍生物,可促进蛋白质合成,增加葡萄糖利用率,也可利于乙酰胆碱的合成,刺激多巴胺的释放,提高脑内能力,改善脑内代谢作用。另外吡拉西坦又可直接作用于大脑皮质,修复受损神经细胞,对缺血缺氧所致的逆行性健忘有积极作用,能够降低缺血所致的乳酸堆积,减轻酸中毒,缩小脑梗死灶体积,增强大脑记忆能力,提高学习效率。动物试验发现[16],吡拉西坦能够改善大鼠脑缺血所致的认知功能障碍,保护神经元损伤。药理学研究报道[17],吡拉西坦能够透过血脑屏障,具有副作用少、毒性低等特点。但有研究发现[18],较单独用药,吡拉西坦联合用药有一定优势,本研究也发现部分患者应用吡拉西坦治疗后疗效判定为无变化或恶化,难以达到满意的治疗效果。

神经生长因子为神经肽类物质,在脑内广泛分布,能够增加神经元兴奋性,利于髓磷脂的修复,对神经的生长、发育和分化有重要作用,且可改善神经退行性改变,促进局部受损神经的修复,减少神经元凋亡,是神经修复机制之一。基础研究证实[19],鼠神经生长因子为近年来研发的神经修复剂,主要来源于小鼠颌下腺,能够利于神经元发育,提高神经递质的敏感性,促进受损纤维再生,减轻脑部神经纤维受损。据文献报道[20],鼠神经生长因子具有调节钙平衡、对抗自由基作用,从而减轻脑缺血缺氧所致的脑水肿及组织损伤,起到脑保护作用。Gudasheva TA 等[21]研究发现,鼠神经生长因子可显著改善小儿缺血缺氧性脑病的神经发育。本研究结果显示,吡拉西坦联合鼠神经生长因子组总有效率相对较高,且治疗后 NISSS 及 ALD 评分改善更明显,说明二者联合治疗能够提高疗效,更有利于神经功能的恢复,从而提高生活质量。可能原因为外源性鼠神经生长因子可进入中枢神经系统,和受体结合为神经修复提供营养因子,加上鼠神经生长因子又可抑制神经元凋亡,利于血管再生,从而提高疗效,利于神经功能的改善[27]。

急性缺血性脑卒中的发病机制复杂,临床研究认为[22],血液中多种物质对维持机体正常内环境有重要作用。近年来研究报道,Hcy 是心脑血管疾病发生的独立危险因素,Hcy 为蛋氨酸代谢的产物,能够激活机体炎症反应,刺激内皮细胞凋亡,促进动脉粥样硬化斑块形成。另外 Hcy 浓度过高可引起脂代谢异常,增加泡沫细胞,增加血管壁厚度,进一步参与动脉粥样硬化形成。高 Hcy 又可促进血小板黏附及聚集,对机体凝血纤溶动态反应产生影响,参与血栓形成。相关研究表明[23],随着脑卒中病灶大小、部位及病情的改变,Hcy 可产生相应变化。Zheng X 等研究报道[24],急性缺血性脑卒中高 Hcy 组结局不良发生率明显低于低 Hcy 组。又有研究表明[25],急性缺血性脑卒中所致的缺血缺氧能够引起应激反应,导致继发性脑损伤,脑血流的中断及再灌注损伤为快速级联反应,可引起炎症反应,导致神经功能损伤。脑损伤后可刺激机体产生局部或者全身炎症反应,诱导 PCT 的表达,其浓度和组织受损程度有良好相关性,机体出现创伤时可增加血清 PCT 浓度。皮质醇为机体应激反应的典型指标,急性缺血性脑卒中发生后可引起保护性应激反应,促进皮质醇的分泌,另外脑缺血能够引起下丘脑受损,导致负反馈调节机制紊乱,增加皮质醇浓度。有关研究认为[26],缺血性脑卒中早期皮质醇水平上升程度和运动障碍、意识障碍程度有关,可作为评价病情及预后的参考指标。本研究结果发现,治疗前患者 Hcy、PCT 及皮质醇浓度相对较高,治疗后以上指标水平均下降,但联合治疗组相对较低,提示二者联合治疗可下调以上指标的表达,促进神经营养因子的表达,从而利于神经功能的修复。另外本研究数据显示,联合治疗组治疗后脑血流学指标变化更明显,进一步证实二者联合治疗的作用,可有效改善脑部血液代谢,促进神经功能的恢复。

综上所述,吡拉西坦联合鼠神经生长因子能够提高急性缺血性脑卒中的疗效,降低 Hcy、PCT 及皮质醇水平,促进神经功能的恢复。但本研究样本量较小,需进一步加大样本例数,减少随机误差,提高结论的可靠性。

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