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吡拉西坦联合胞磷胆碱对急性脑梗死认知功能和神经功能的影响 *

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摘要 目的:研究吡拉西坦联合胞磷胆碱对急性脑梗死认知功能和神经功能的影响。**方法:**选择 2014 年 1 月～2018 年 1 月我院的 150 例急性脑梗死患者,随机分为两组。对照组采用吡拉西坦治疗,观察组采用吡拉西坦联合胞磷胆碱治疗。采用神经功能缺损程度(National Institutes of Health Stroke Scale,NIHSS)、析蒙特利尔认知评估量表(Montreal cognitive assessment scale,Mo CA)和日常生活能力(Activities of daily living,ADL)评分量表,比较两组治疗前后神经功能、认识功能和日常生活能力变化。**结果:**观察组基本治愈 15 例,显效 30 例,有效 26 例,无效 4 例,恶化 1 例,总有效率为 94.67%,明显高于对照组(P<0.05);治疗后,两组的 ADL 和 Mo CA 评分明显升高,神经功能缺损量表(National Institutes of Health Stroke Scale,NHISS)评分明显降低,且观察组的 ADL、Mo CA 和 NHISS 评分明显优于对照组(均 P<0.05);治疗后,两组的血清细胞凋亡蛋白酶 -3(cysteinyl aspartate specific proteinase-3,Caspase-3)和低氧诱导因子 -1α(Hypoxia-inducible factor 1 α,HIF-1α)水平均明显降低,且观察组明显低于对照组(均 P<0.05);对照组发生干呕 1 例(1.33%),恶心 2 例(2.67%),头痛 1 例(1.33%),头晕 1 例(1.33%);观察组发生干呕 1 例(1.33%),恶心 1 例(1.33%),头痛 1 例(1.33%),出血 1 例(1.33%);两组无明显差异(P>0.05)。**结论:**吡拉西坦联合胞磷胆碱能改善急性脑梗死的认知功能和神经功能,其机制可能与调节细胞诱导因子 Caspase-3 和 HIF-1α 的表达水平相关。

关键词:吡拉西坦;胞磷胆碱;急性脑梗死;认知功能;神经功能
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Effects of Piracetam Combined with Citicoline on Cognitive and Neurological Functions in Patients with Acute Cerebral Infarction*

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ABSTRACT Objective: To study the effect of piracetam combined with citicoline on cognitive and neurological functions in patients with acute cerebral infarction. **Methods:** 150 patients with acute cerebral infarction from January 2014 to January 2018 were randomly divided into two groups. The control group was treated with piracetam, and the observation group was treated with piracetam combined with citicoline. Using the National Institutes of Health Stroke Scale (NIHSS), the Montreal Cognitive Assessment Scale (Mo CA), and the Activities of Daily Living (ADL) rating scale, coomparison of neurological function, cognitive function and daily living ability before and after treatment in the two groups. **Results:** In the observation group, 15 cases were basically cured, 30 cases were markedly effective, 26 cases were effective, 4 cases were ineffective and 1 case was deteriorated. The total effective rate was 94.67%, which was higher than that in the control group (P<0.05). After treatment, the ADL, Mo CA and NHISS scores of the two groups increased significantly, and the ADL, MoCA and NHISS scores of the observation group were significantly better than those of the control group (all P<0.05). After treatment, the levels of serum Caspase-3 and HIF-1alpha in two groups were significantly decreased, and the levels of serum Caspase-3 and HIF-1alpha in the observation group were lower than those in the control group (all P<0.05). The control group had 1 case of retching (1.33%), 2 cases of nausea (2.67%), 1 case of headache (1.33%) and 1 case of dizziness (1.33%), the observation group had 1 case of retching (1.33%), 1 case of nausea (1.33%), 1 case of headache (1.33%) and 1 case of haemorrhage (1.33%), there was no differ-

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ence between the two groups (P>0.05). **Conclusion:** Piracetam combined with citicoline can significantly improve cognitive and neurological functions in patients with acute cerebral infarction. Miracles may be related to the expression of Caspase-3 and HIF-1a.

Key words: Piracetam; Citicoline; Acute cerebral infarction; Cognitive function; Neurological function

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前言

随着我国人民生活水平的迅速提高,加上人口老龄化的加剧,每年均会出现大量的急性脑血管疾病病例,其发病率大约为 0.72 %~0.75 %[1]。急性脑梗死主要表现为脑血管的管壁有所狭窄甚至闭塞, 导致脑组织的血供不足和脑血流受到阻塞,致死率极高[2,3]。临床治疗该病的重点在于促进缺血区的血液灌注快速恢复,开通患者的侧支循环,进而使脑组织供血供氧的能力增强,减轻脑细胞受损程度[4,5]。临床上以溶栓疗法为主,但是其治疗的有效率比较低,发生颅内出血的风险较大,而且通常难以掌握最佳的治疗时机。吡拉西坦能减轻脑部的缺氧损伤,促进受损大脑的恢复[6]。胞磷胆碱钠主要通过降低脑血管的阻力,加速脑物质的代谢,从而改善脑循环[7]。由于急性脑梗死的病理生理变化比较复杂,故单一用药的疗效并不满意,需给予综合治疗。吡拉西坦联合胞磷胆碱治疗高血压脑出血患者神经功能恢复的影响,国内外对研究较多,但是在急性脑梗死治疗后神经功能的恢复中的应用目前国内很少,为了论证吡拉西坦以及胞磷胆碱联合使用在急性脑梗死治疗中的优越性,本研究自 2014 年 1 月～2018 年 1 月, 选取了 150 例患者进行治疗,并观察其对认知功能和神经功能的影响,现报告如下。

1 资料与方法

1.1 一般资料

选择 2014 年 1 月～2018 年 1 月我院的 150 例急性脑梗死患者,均符合相关的诊断标准;40~85 岁的住院患者,性别不限;均知情同意;经颅脑 CT 平扫检查均未发现出血、颅内感染和肿瘤。排除标准:合并代谢性疾病或重症感染;既往有重大疾病史或肝肾等脏器恶性病史;合并恶性肿瘤;有沟通障碍者。用抽签法随机分为两组。观察组 75 例,男 42 例,女 33 例;年龄 40~85 岁,平均 (63.72± 6.29) 岁;脑梗死的部位:基底节 34 例,脑叶 31 例,小脑 10 例。对照组 75 例,男 45 例,女 30 例;年龄 40~85 岁,平均 (62.45± 7.13) 岁;脑梗死的部位:基底节 35 例,脑叶 30 例,小脑 10 例。两组的基线资料具有可比性。

1.2 方法

两组均给予抗血小板聚集,预防感染,维持水电解质平衡,控制患者血压、血糖,保护神经,降低颅内压,吸氧、纠正酸碱和补液等常规的疗法。对照组:静脉滴注吡拉西坦注射液(山东威高药业股份有限公司,国药准字 H20073420,规格:50 mL/ 瓶),每次 100 mL,每天 1 次。观察组:在吡拉西坦的给药基础上,口服胞磷胆碱钠胶囊(齐鲁制药有限公司,国药准字 H20020220,规格:0.1 g/ 粒),每次 0.2 g,每天 3 次。均治疗 4 w。

1.3 观察指标

疗效标准[8]:① 基本治愈:患者的病残程度为 0 级,NHISS 评分降低≥ 91 %;② 显效:患者的病残程度为 1～3 级,46 %≤ NHISS 评分降低的幅度≤ 90 %;③ 有效:18 %≤ NHISS 评分降低的幅度≤ 45 %;④ 无效:NHISS 评分升高或降低的幅度≤ 17 %;⑤ 恶化:NHISS 评分升高的幅度＞18 %。

治疗前后,用 NHISS、Mo CA 和 ADL 判断神经功能、认识功能和日常生活能力。ADL 量表包括洗澡、进食、修饰洗刷、大便控制、穿衣、小便控制、床 - 椅转移、用厕和平地行走等项目,评分值为 14～56 分。NHISS 量表包括凝视、意识水平、视野、上肢运动、面瘫、下肢运动、感觉、共济失调、语言、忽视症以及构音障碍等项目,其中评分 0～15 分表示轻型,评分 16～30 分表示中型,评分 31～45 分表示重型。Mo CA 量表包括视结构技能、交替连线测验、命名、注意、记忆、暗示、词语流畅性、句子复述、抽象、定向和延迟回忆等,满分为 30 分。

治疗前和治疗后 4 w, 采集患者清晨空腹静脉血 3 mL,用 ELISA 法检测血清 Caspase-3 和 HIF-1α 水平,试剂盒购自南京森贝伽生物公司。

并观察两组呕吐、恶心、头痛和出血等不良反应情况。

1.4 统计学分析

采用 SPSS 20.0 统计软件,计量数据以($\bar{x}$± s),计数数据以%表示, 对比采用 t 检验与卡方分析, 检验水准为α=0.05, P<0.05 为存在统计学意义。

2 结果

2.1 疗效对比

观察组基本治愈 15 例,显效 30 例,有效 26 例,无效 4 例,恶化 1 例,总有效率为 94.67%,明显高于对照组(P<0.05),见表1。

表 1 疗效对比[例(%)]

Table 1 Comparison of the clinical effect [n(%)]

Groups	n	Basic cure	Effective	Valid	Invalid	Deteriorate	The total effect rate
Control group	75	10(13.33)	26 (34.67)	21(28.00)	15(20.00)	3(4.00)	76.00
Observation group	75	15(20.00)	30(40.00)	26(34.67)	4(5.33)	1(1.35)	94.67*

Note: Compared with the control group, *P<0.05.

2.2 ADL、Mo CA 和 NHISS 评分对比

治疗后，两组的 ADL 和 Mo CA 评分明显升高，NHISS 评分明显降低，且观察组的 ADL、Mo CA 和 NHISS 评分明显优于对照组(均 $P<0.05$)，见表 2。

表 2 ADL、Mo CA 和 NHISS 评分对比($\bar{x}\pm s$，分)

Table 2 Comparison of ADL, Mo CA and NHISS scores($\bar{x}\pm s$, scores)

Groups	n	ADL scores		Mo CA scores		NHISS scores	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	75	32.75± 6.39	42.51± 10.63#	14.76± 3.12	16.59± 5.32#	19.27± 3.16	15.17± 2.03#
Observation group	75	31.89± 6.43	56.38± 12.79*#	14.93± 3.27	19.32± 6.34*#	19.33± 2.76	10.03± 1.25*#

Note: Compared with the control group, *$P<0.05$; compared with before treatment, #$P<0.05$.

2.3 血清 Caspase-3 和 HIF-1α 水平对比

治疗后，两组的血清 Caspase-3 和 HIF-1α 水平均明显降低，且观察组上述指标的变化更显著(均 $P<0.05$)，见表 3。

表 3 血清 Caspase-3 和 HIF-1α 水平对比($\bar{x}\pm s$)

Table 3 Comparison of serum Caspase-3 and HIF-1alpha levels($\bar{x}\pm s$)

Groups	n	Caspase-3 (U/L)		HIF-1α(ng /L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	75	55.37± 12.48	40.13± 10.75#	323.46± 24.78	291.37± 20.45#
Observation group	75	54.29± 11.63	16.35± 4.62*#	324.51± 23.64	161.34± 13.25*#

2.4 不良反应

对照组发生干呕 1 例(1.33%)，恶心 2 例(2.67%)，头痛 1 例(1.33%)，头晕 1 例(1.33%)；观察组发生干呕 1 例(1.33%)，恶心 1 例(1.33%)，头痛 1 例(1.33%)，出血 1 例(1.33%)；两组无明显差异($P>0.05$)。

3 讨论

急性脑梗死是一种由微小血管血栓形成和动脉粥样硬化血栓等多种因素引发的神经内科疾病，发病率占脑卒中的 70% 以上[8]。其发病机制与组织缺氧、血液黏度增高、炎症因子等有关[9-11]。急性脑梗死在发作时，病人脑血管内液的粘稠度明显升高，使血流阻力增加，血流的速度减慢，微循环发生障碍，使得脑组织细胞快速发生能量代谢障碍，造成神经胶质衰竭以及神经元衰竭，因而改善上述的症状是治疗该病的有效途径[12-15]。溶栓为首要治疗方案，但溶栓时机的把握、脑出血等并发症，严重影响疗效[16]。

吡拉西坦作为常用的一种脑代谢活化剂，可以使脑细胞的葡萄糖利用率以及 ATP/ADP 比率明显升高，改善神经细胞的能量衰竭情况，从而促进脑神经细胞不断修复[17-19]。有研究发现，吡拉西坦可以增强神经细胞对于缺氧的耐受程度，明显升高神经细胞的存活率[20]。而且，吡拉西坦可以改善脑组织的血液供应状态，使脑部左右半球的神经信息传递速度加快。胞磷胆碱可以有效抑制脑缺血后的自由基及脂质过氧化物的生成，改善脑部的血液循环[21,22]。胞磷胆碱能抑制脑缺血后脂质过氧化物氧以及自由基的生成，还能改善血液循环，增加脑部的血流量，明显减轻缺血性脑损伤后出现的神经功能缺损[23-25]。本研究发现，观察组的 ADL、Mo CA 和 NHISS 评分明显优于对照组；表明吡拉西坦和胞磷胆碱通过二者作用效果的联合，改善生活能力、认知功能和神经功能。

研究表明，在细胞的凋亡和坏死过程中，需要凋亡蛋白酶的分解以及诱导因子的激活一起发挥作用[26]。溶栓疗法仅改善血流供应，无法对细胞诱导因子 Caspase-3 和 HIF-1α 发挥调控和抑制的效果，因此较难控制疾病的进展，影响治疗效果，而且后期的复发率极高[27-29]。研究发现，胞磷胆碱能抑制细胞凋亡蛋白酶和缺氧诱导因子的合成与表达，能降低机体调控因子的表达水平，减轻对正常脑细胞产生的刺激，降低其对机体脑细胞造成的损伤，改善脑部的代谢，促进脑部正常生理功能的修复[30]。本研究观察组的血清 Caspase-3 和 HIF-1α 水平明显低于对照组。表明其原因为，吡拉西坦联合胞磷胆碱能有效调节细胞诱导因子 Caspase-3 和 HIF-1α 的表达水平。吡拉西坦联合胞磷胆碱可以抑制蛋白酶和凋亡诱导因子，加快脑代谢和循环的速度，在确保脑组织有充足的血氧供应，减轻诱导因子对脑细胞的桑伤害，而且保护并加速药物对脑组织的修复功能，降低致残率。

综上，吡拉西坦联合胞磷胆碱能改善急性脑梗死的认知功能，神经功能，其机制会可能与调节细胞诱导因子 Caspase-3 和 HIF-1α 的表达水平相关。

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