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丁苯酚联合尼莫地平对急性脑出血患者神经功能及血清 MMP-9、NF- κ B 水平的影响 *

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摘要 目的: 探讨丁苯酚联合尼莫地平对急性脑出血患者及神经功能及血清基质金属蛋白酶 9 (MMP-9) 和核转录因子 kappa B (NF- κ B) 水平的影响。**方法:** 选择 90 例急性脑出血患者作为研究对象并将其随机分为两组, 每组各 45 例。两组患者均给予口服尼莫地平片治疗, 观察组在对照组基础上加以口服丁苯酚软胶囊, 疗程均为 30 天。比较两组患者的临床疗效以及治疗前后血清 MMP-9、NF- κ B 水平和神经功能的变化。**结果:** 观察组患者的临床总有效率显著高于对照组 [42(93.99%) vs 37(82.22%)] ($P < 0.05$)。治疗后, 观察组的血清 MMP-9、NF- κ B 水平均明显低于对照组 [121.51 ± 14.76 vs 137.09 ± 14.71 ; 0.14 ± 0.04 vs 0.24 ± 0.05] ($P < 0.05$), 日常生活质量评分(ADL)明显高于对照组 [37.09 ± 5.91 vs 33.54 ± 6.74] ($P < 0.05$), 神经功能缺损评分(NIHSS)明显低于对照组 [15.31 ± 7.61 vs 18.54 ± 5.21] ($P < 0.05$), 认知功能评分(MMSE)明显高于对照组 [27.54 ± 4.21 vs 23.72 ± 5.75] ($P < 0.05$)。**结论:** 丁苯酚联合尼莫地平治疗急性脑出血患者的临床疗效优于口服尼莫地平片单药治疗, 可有效改善患者的神经和认知功能, 可能与其显著降低血清 MMP-9、NF- κ B 水平有关。

关键词: 丁苯酚; 尼莫地平; 急性脑出血; 基质金属蛋白酶 9; 核转录因子 kappa B

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Effect of D1-3-butylphthalide Combined with Nimodipine on the Serum of MMP-9, NF- κ B Levels and Neurological Function of Patients with Acute Cerebral Hemorrhage*

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ABSTRACT Objective: To investigate the effect of D1-3-butylphthalide combined with nimodipine on the Serum of MMP-9, NF- κ B levels and Neurological function of Patients with Acute Cerebral Hemorrhage. **Methods:** 90 cases of patients with acute cerebral hemorrhage were selected as the research object and randomly divided into two groups, 45 cases in each group. Both groups of patients were given oral nimodipine treatment, the observation group was given butyl phenol on the basis of control group, 30 days was considered as a treatment cycle. The clinical efficacy, changes of serum levels of MMP-9, NF-kappa B and neurological function before and after treatment were compared between two groups. **Results:** The total effective rate of observation group was significantly higher than that of the control group (93.99% vs 37 82.22%)] ($P < 0.05$). After treatment, the serum levels of MMP-9, NF-kappa B of observation group were significantly lower than those of the control group (121.51 ± 14.76 vs. 137.09 ± 14.71 ; 0.14 ± 0.04 vs. 0.24 ± 0.05) ($P < 0.05$), the quality of life scale (ADL) was significantly higher than that of the control group (37.09 ± 5.91 vs. 33.54 ± 6.74) ($P < 0.05$), and the neurological function defect score (NIHSS) scores was significantly lower than the control group (15.31 ± 7.61 vs 18.54 ± 5.21) ($P < 0.05$), the cognitive function score (MMSE) was significantly higher than that of the control group (27.54 ± 4.21 vs 23.72 ± 5.75] ($P < 0.05$). **Conclusion:** D1-3-butylphthalide combined with nimodipine was more effective than nimodipine alone in the treatment of acute cerebral hemorrhage patients, it could effectively improve the neurological and cognitive function, which might be related to the reduction of serum levels of MMP-9, NF-kappa B.

Key words: D1-3-butylphthalide; Nimodipine; Acute cerebral hemorrhage; MMP-9; NK- κ B

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前言

脑出血是目前最常见的神经内科疾病之一,其发病率和死亡率均较高,据统计急性期病死率为 30%~40%^[1,2]。有研究表明脑出血的病理有三个关键阶段,分别是早期脑血管破裂、脑部患处血肿的形成和扩大以及血肿周围出现水肿,以上三个阶段标志着患者病情逐渐严重^[3]。口服尼莫地平是目前临床上较常用的一种治疗脑出血的方法,尼莫地平能够有效的降低钙离子的浓度,阻止钙离子的内流,促进血管平滑肌松弛,进而改善脑血管痉挛,缓解脑血对流^[4,5]。丁苯酚作为我国自主研发的一种化学合成类药物,能有效改善神经功能损伤,促进神经细胞的修复^[6]。因此,本研究主要采用丁苯酚联合尼莫地平的治疗急性脑出血患者,探讨临床疗效及可能机制,结果报道如下。

1 资料与方法

1.1 一般资料

选择 2014 年 9 月至 2016 年 3 月在我院接受治疗的 90 例急性脑出血患者(男 41 例,女 49 例)作为研究对象。按照随机数字法分配为对照组和观察组,每组各 45 例。对照组中,男 16 例,女 29 例,年龄 39~70 岁,平均(46.88±4.41)岁;观察组中,男 21 例,女 24 例,年龄 41~76 岁,平均(48.31±4.69)岁。两组患者的一般临床资料比较差异均无统计学意义($P>0.05$),具有可比性。纳入标准:诊断标准符合全国脑血管病学会会议制定的诊断标准^[7]。排除标准:①无药物过敏史,②不存在外伤、感染等症状,③无心、肝、肾等其他脏器功能异常情况,④糖尿病和手术治疗者。本次研究所有患者及其家属均已知情,且本次研究已在我院伦理委员会批准下实施。

1.2 治疗方法

两组患者在入院后予以颅内止血、降压等基础治疗措施,对照组患者给予口服尼莫地平缓释片(江苏康缘药业股份有限公司,国药准字 H20066423,60 mg×10 s),每次 2 片(120 mg),一日 2 次。观察组在对照组的基础上增服丁苯酚软胶囊(石药集团恩必普药业有限公司,国药准字 H20050299,0.1 g×24 s),空腹口服,一日 3 次,一次 2 粒(0.2 g),两组患者疗程为 30 d。

1.3 观察指标

①比较两组患者的临床疗效,分为基本治愈、显著进步、进步和无效等四个等级;②使用简易精神状态检查表(Mini-Mental State Examination)^[8]、日常生活能力量表(Activity of Daily Living Scale, ADL)^[9]对患者进行治疗前后的认知状况和日常生活能力评分,评分越高表示患者恢复状况越好,同时使用神经功能缺损量表(National Institute of Health stroke scale, NIHSS)^[9]对患者进行治疗前后情况的评分,NIHSS 分数越高,表明神经功能缺损越严重;③采用酶联免疫吸附实验法(ELISA)测定血清 MMP-9 水平;④采用核因子- κ B(NF- κ B)试剂盒(Abnova)测定患者血清核因子- κ B 水平。

1.4 统计学分析

数据采用 spss19.0 软件包进行处理,两组计数资料的对比采用 χ^2 检验,计量资料采取均数±标准差($\bar{x} \pm s$)表示,两组间比较采用 t 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者临床疗效的对比

治疗后,对照组的总有效率为 37(82.22%),观察组的总有效率为 42(93.99%),观察组患者总有效率显著高于对照组($P<0.05$),见表 1。

表 1 两组患者临床疗效的比较(例,%)

Table 1 Comparison of the clinical efficacy between two groups(n,%)

Group	n	Basic cure	Markedly	Effective	Invalid	Total efficiency
Control group	45	7(15.56)	16(35.56)	14(31.11)	8(17.77)	37(82.22)
Observation group	45	11(24.44)	24(53.33)	7(15.56)	3(6.67)	42(93.99)

Note: * $P<0.05$ compared with the control group.

2.2 两组患者治疗后不同时点血清 MMP-9 水平的变化比较

两组患者在经过治疗后,血清 MMP-9 水平在治疗后 7 d

后达到高峰,而后下降。观察组治疗后 12 h、24 h、7 d 和 14 d 血清 MMP-9 水平均明显低于对照组($P<0.05$),见表 2。

表 2 两组治疗后不同时点血清 MMP-9 水平的变化比较(mmol/L, $\bar{x} \pm s$)

Table 2 Comparison of the serum MMP-9 levels between two groups at different time points after treatment(mmol/L, $\bar{x} \pm s$)

Group	n	12 h	24 h	7 d	14 d
Control group	45	46.57±2.14	77.31±6.57	257.29±16.33	137.09±14.71
Observation group	45	49.33±2.27	68.12±6.07	238.81±9.87	121.51±14.76
P value		<0.05	<0.05	<0.05	<0.05

2.3 两组患者治疗前后 ADL 的比较

治疗后,两组患者的 ADL 评分较治疗前均明显上升,且观察组患者的 ADL 评分明显高于对照组(37.09±5.91 vs 33.54±6.74) ($P<0.05$),见表 3。

2.4 两组患者治疗前后 NIHSS 和 MMSE 的比较

治疗后,两组患者 NIHSS 评分均较治疗前显著降低($P<0.05$),而 MMSE 评分均较治疗前明显升高($P<0.05$),且观察组治疗后 NIHSS 评分显著低于对照组($P<0.05$),MMSE 评分明显高于对照组($P<0.05$),见表 4。

表 3 两组患者治疗前后日常生活质量评分(ADL)的比较(分, $\bar{x} \pm s$)Table 3 Comparison of the ADL score between two groups before and after treatment(points, $\bar{x} \pm s$)

Group	n	Before treatment	After treatment	T value	P value
Control group	45	26.75 $\pm$ 6.24	33.54 $\pm$ 6.74	4.9590	<0.05
Observation group	45	24.39 $\pm$ 5.47	37.09 $\pm$ 5.91	10.5793	<0.05
P value		>0.05	<0.05		

表 4 两组患者治疗前后 NIHSS 和 MMSE 比较(分, $\bar{x} \pm s$)Table 4 Comparison of the NIHSS and MMSE before and after treatment between two groups(points, $\bar{x} \pm s$)

Group	NIHSS		P value	MMSE		P value
	Before treatment	After treatment		Before treatment	After treatment	
Control group	22.59 $\pm$ 7.46	18.54 $\pm$ 5.21	<0.05	19.17 $\pm$ 4.86	23.72 $\pm$ 5.75	<0.05
Observation group	22.45 $\pm$ 6.87	15.31 $\pm$ 7.61	<0.05	19.36 $\pm$ 5.37	27.54 $\pm$ 4.21	<0.05
P value	>0.05	<0.05		>0.05	<0.05	

2.5 两组患者治疗前后血清核因子- κ B(NF- κ B)的水平比较

治疗后, 所有患者的血清 NF- κ B 指水平均较治疗前明显

下降, 且观察组血清 NF- κ B 水平明显低于对照组($P < 0.05$), 见表 5。

表 5 两组患者治疗前后血清核因子- κ B(NF- κ B)的水平比较(mmol/L, $\bar{x} \pm s$)Table 5 Comparison of the serum NF- κ B level between two groups before and after treatment(mmol/L, $\bar{x} \pm s$)

Group	n	Before treatment	After treatment	P value
Control group	45	0.40 $\pm$ 0.07	0.24 $\pm$ 0.05	<0.05
Observation group	45	0.39 $\pm$ 0.06	0.14 $\pm$ 0.04	<0.05
P value		>0.05	<0.05	

3 讨论

脑出血病情进展迅速且并发症较多, 急性脑出血后出现的颅内压升高、颅内血肿和脑水肿都会导致占位效应, 是影响神经功能的重要原因^[11,12]。而急性脑出血后造成脑内缺氧、缺血等原因导致自由基增多, 诱发广泛的炎症反应, 对患者身心都造成严重的影响^[13]。

MMP-9 是一种由于脑细胞缺血缺氧导致激活 MMPs 系统刺激中性粒细胞以及巨噬细胞分泌形成的促炎蛋白酶, 可反映脑出血患者血肿周围水肿的情况, MMP-9 水平越高, 提示患者血肿周围的水肿情况越严重^[13,14]。核因子- κ B 作为一种重要的核转录因子存在于脑血管内皮、神经元和胶质细胞中, 当脑出血后核因子- κ B 被激活, 进一步促进了炎症反应、细胞程序性死亡(PCD)以及自由基的损伤^[15]。

丁苯酚是一种化学合成类药物, 能够透过患者因急性脑出血形成的血脑屏障直接作用于脑部出血部位, 并有选择性的将药力释放至患者的脑组织内部^[16]。丁苯酚在一定程度上可以减轻组织水平和炎症反应, 抑制神经细胞的凋亡^[17], 另一方面, 丁苯酚同尼莫地平具有相同的作用, 可以降低钙离子浓度, 降低钙离子浓度将有效抑制自由基的产生, 从而减轻炎症反应和过氧化反应, 患者的神经细胞也得到恢复^[18,19]。目前研究表明丁苯酚还能与患处缺血区域的脑线粒体发生反应, 使患处脑线粒体结构和功能提升, 进而提升患处的血液流速和容量, 有效改善脑部缺血症状, 在滋养脑部神经过程中进一步提升脑神经的功能, 对神经功能提供了保护屏障^[20,21]。尼莫地平作为目前脑出血

临床上的常用药, 对钙离子的流通起到阻滞功能, 能有效地通过血脑的屏障, 对脑血管及神经细胞进行选择性的作用, 缓解患处缺血和选择性扩张血管的作用, 在一定程度上促使血管平滑肌松弛, 改善了脑血流, 对缓解脑血肿和周围水肿有一定积极的作用^[22]。

本研究中, 观察组在对照组的基础上增加了丁苯酚的治疗方式, 观察组临床总有效率明显高于对照组, 而血清 MMP-9 的指标水平明显低于对照组, 说明该治疗方式能更好的抑制 MMPs 系统的激活, 从而缓解脑出血患处的炎症反应、血肿周围水肿和血脑屏障等。同时, 观察组的血清核因子- κ B 水平明显低于对照组, 证明丁苯酚联合尼莫地平有效的抑制了 NF- κ B 的表达, 减缓炎症反应, 从而缓解脑缺血与水肿, 更有效的改善患者的症状。针对两组患者进行日常生活质量评分(ADL)、神经功能缺损评分(NIHSS)和认知功能评分(MMSE)统计结果显示: 患者在治疗的认知能力和神经功能的情况均得到明显恢复, 而观察组患者在三项评分统计中更加优于对照组患者, 这一结果说明丁苯酚联合尼莫地平的治疗方式对比单独使用尼莫地平的治疗方式能更好的对急性脑出血患者的神经功能进行保护和恢复。

综上所述, 丁苯酚联合尼莫地平治疗急性脑出血患者的临床疗效优于口服尼莫地平片单药治疗, 可有效改善患者的神经和认知功能, 可能与其显著降低血清 MMP-9、NF- κ B 水平有关。

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