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脑心通胶囊联合神经生长因子治疗高血压脑出血的疗效及对血清 IL-6、MMP-9、S100B 水平的影响 *

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摘要 目的：研究脑心通胶囊联合神经生长因子治疗高血压脑出血的疗效及对血清白介素 -6(IL-6)、基质金属蛋白酶 -9(MMP-9)、S100B 水平的影响。**方法：**选取 2015 年 8 月至 2016 年 7 月本院收治的 88 例高血压脑出血患者，根据患者入院顺序分为观察组和对照组，44 例每组。对照组使用神经生长因子治疗，观察组使用脑心通胶囊联合神经生长因子进行治疗。比较两组患者临床疗效，治疗前后 GCS、GOS 评分、血清 IL-6、MMP-9、S100B 水平的变化。**结果：**治疗后，观察组临床总有效率显著高于对照组(P<0.05)。两组患者治疗后 GCS、GOS 评分均较治疗前明显升高(P<0.05)，血清 IL-6、MMP-9、S100B 水平均较治疗前显著降低(P<0.05)，且观察组的 GCS、GOS 评分显著高于对照组(P<0.05)，血清 IL-6、MMP-9、S100B 水平明显低于对照组(P<0.05)。所有患者用药期间均未发生药物不良反应。**结论：**脑心通胶囊联合神经生长因子治疗高血压脑出血的疗效肯定，且能有效降低患者血清 IL-6、MMP-9、S100B 水平，安全性高。

关键词：脑心通胶囊；神经生长因子；高血压脑出血；血清白介素 -6；基质金属蛋白酶 -9；S100B

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Effect of Naoxintong Capsule Combined with Nerve Growth Factor in Treatment of Hypertensive Cerebral Hemorrhage and Its Effect on Serum Levels of IL-6, MMP-9 and S100B*

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ABSTRACT Objective: To study the effect of naoxintong capsules combined with nerve growth factor on the serum levels of interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and S100B of patients with hypertensive intracerebral hemorrhage. **Methods:** 88 patients with hypertensive intracerebral hemorrhage who were treated in our hospital from August 2015 to July 2016 were selected and randomly divided into the observation group and the control group The patients in the control group were treated with nerve growth factor, while the patients in the observation group were treated with naoxintong capsules combined with nerve growth factor. Then the clinical efficacy, GCS, GOS score, serum levels of IL-6, MMP-9 and S100B were observed and compared between the two groups. **Results:** After treatment, the total effective rate in the observation group was significantly higher than that the control group (P<0.05). After treatment, the GCS and GOS scores of the two groups were significantly higher than before, and the GCS and GOS of the observation group were higher than those of the control group (P<0.05). After treatment, the serum levels of IL-6, MMP-9 and S100B in the two groups were significantly lower than before, and the observation group were lower than those of the control group (P<0.05). There was adverse reactions in the two groups. **Conclusion:** Naoxintong capsule combined with nerve growth factor can reduce the serum levels of IL-6, MMP-9 and S100B in patients with hypertensive intracerebral hemorrhage, with obvious clinical curative effect and high safety.

Key words: Naoxintong capsule; Nerve growth factor; Hypertensive intracerebral hemorrhage; Serum interleukin -6; Matrix metalloproteinase -9; S100B

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前言

脑出血是一种临床较为常见的疾病，约占在所有入院患者的 20%左右，有着较高的致残率、病死率，远期预后较差[1]。高血压是在非创伤性颅内出血最为常见的一种病因，主要是指高血压病发生小动脉病变，因血压骤升而发生的动脉破裂出血，在脑出血中属于较为常见的一种类型[2]。当高血压脑出血血肿量低于 30 mL 时大多数以保守治疗为主，但会因为周围组织的水肿、缺血，血肿的压迫，及出血后血红蛋白细胞毒性及凝血酶的作用，患者的神经功能障碍难以恢复。既往研究表明神经生长

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因子能缓解脑组织损伤、促使神经功能恢复、保护神经元等[3]。脑心通胶囊经益气活血化瘀的作用能促使血液的凝、聚、黏、浓及微循环障碍得到改善[4]。因此,本研究主要就脑心通胶囊联合神经生长因子治疗高血压脑出血的疗效及对血清白介素 -6(IL-6)、基质金属蛋白酶 -9(MMP-9)、S100B 的影响进行了分析。

1 资料与方法

1.1 临床资料

选取 2015 年 8 月至 2016 年 7 月本院收治的 88 例高血压脑出血患者。纳入标准:① 所有患者均经 MRI 或 CT 检查得以确诊;② 发病至入院均是在 24 h 以内;③ 依从性较差,难以配合医护人员完成本次试验;④ 均未使用过抗凝药物。排除标准:① 严重心、肝、肾功能障碍者;② 精神疾病史;③ 肺部感染者;④ 脑肿瘤卒中。研究均在患者及其家属的知情同意下完成,同时得到了我院伦理委员会的批准和实施。根据患者入院顺序将所有患者分为观察组和对照组两组,44 例每组。其中观察组中男性 28 例,女性 16 例;年龄为 45~80 岁,平均(64.98± 4.02)岁;发病至入院时间 0.8~8.3 h,平均(4.34± 1.02)h。对照组中男性 25 例,女性 19 例;年龄为 47~82 岁,平均(65.02± 4.11)岁;发病至入院时间 0.9~8.5 h,平均(4.37± 1.01)h。两组患者性别、年龄、发病至入院时间临床资料比较无统计学差异(P>0.05),具有可比性。

1.2 治疗方法

所有患者入院后均完成抗炎、控制血压、脱水、止血等常规治疗。对照组在常规治疗基础上使用神经生长因子(生产厂家:丽珠集团丽珠制药厂,规格:30 μg/ 瓶,生产批号:20150505),肌肉注射,30 μg/ 次,1 次 / 天。观察组在对照组治疗基础上联合脑心通胶囊 (生产厂家:陕西步长制药有限公司,规格:0.4 g× 18 s× 2 板,生产批号:20150206),口服,2~4 s/ 次,3 次 / 天。所有患者均需连续治疗 1 个月。

1.3 观察指标

1.3.1 疗效评价 经治疗后,患者的语言、肌力、意识功能均恢复至正常,并且生活能自理则为基本治愈;经治疗后,患者的症状及意识障碍明显好转,可完成简单对话,肌力提高 2 级则为显效;经治疗后,患者意识障碍有所好转,症状明显减轻,可发音,肌力提高 1 级则为有效;经治疗后,患者的症状及意识并未得到改变则为无效[5]。

1.3.2 GCS、GOS 评分 比较两组患者治疗前治疗 1 个月后格拉斯哥昏迷指数评分(GCS)、格拉斯哥预后评分(GOS),其中 GCS 包括肢体运动、语言反应、睁眼反应三个方面的评价,其中重度昏迷评分为 3~8 分,中度昏迷评分为 9~12 分,轻度昏迷评分为 13~14 分,分数越高则表明患者意识状态越好。GOS 评分标准为:死亡则为 1 分;处于植物生存状态则为 2 分;重度残疾,但处于清醒状态,日常生活需照料则为 3 分;轻度残疾,但能独立生活则为 4 分;恢复正常生活,恢复良好则为 5 分。

1.3.3 血清 IL-6、MMP-9、S100B 水平检测 分别在治疗前和治疗 1 个月后抽取两组患者 5 mL 的肘静脉血,转速 3000 r/min,离心 15 min,清分离后,放置在 -20 ℃低温箱中待测,使用酶联免疫法检测血清 IL-6、MMP-9、S100B 浓度,由深圳晶美生物工程有限公司提供试剂盒,均根据说明书完成严格执行本次操作。

1.4 统计学处理

本次实验数据处理选择 SPSS 11.5 软件包进行,计量资料用($\bar{x}$± s)来表示,采用 t 检验,计数资料用[n(%)]来表示,采取 x^2 检验,以 P<0.05 表明差异具有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组临床总有效率显著高于对照组[93.18%(41/44)比 65.91%(29/44)](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(%)]

Groups	Cases	Basic cure	Markedly	Effective	Invalid	The total effective
Observation group	44	23(52.27)	11(25.00)	7(15.91)	3(6.82)	41(93.18)*
Control group	44	10(22.73)	5(11.36)	14(31.82)	15(34.09)	29(65.91)

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

2.2 两组患者治疗前后 GCS、GOS 评分比较的比较

治疗前,两组患者 GCS、GOS 评分比较差异均无统计学意义(P>0.05)。治疗后,两组患者 GCS、GOS 评分均较治疗前明显升高(P<0.05),且与对照组相比,观察组的 GCS、GOS 评分明显升高(P<0.05),见表 2。

表 2 两组患者治疗前后 GCS、GOS 评分比较($\bar{x}$± s,分)

Table 2 Comparison of the GCS, GOS scores between two groups before and after treatment($\bar{x}$± s, points)

Items	Observation group(n=44)		Control group(n=44)	
	Before treatment	After treatment	Before treatment	After treatment
GCS	8.32± 0.87	12.03± 0.45*#	8.28± 0.92	10.76± 0.52*
GOS	2.01± 0.23	3.87± 0.34*#	2.04± 0.25	2.49± 0.29*

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

2.3 两组治疗前后血清 IL-6、MMP-9、S100B 水平的比较

治疗前,两组患者血清 IL-6、MMP-9、S100B 水平比较差异无统计学意义(P>0.05)。治疗后,两组患者血清 IL-6、MMP-9、S100B 水平较治疗前显著降低(P<0.05),和对照组相比,观察组

IL-6、MMP-9、S100B 水平较低(P<0.05),见表 3。

表 3 两组治疗前后血清 IL-6、MMP-9、S100B 水平的比较($\bar{x}\pm$ s)

Table 3 Comparison of the IL-6, MMP-9, S100B levels between two groups before and after treatment ($\bar{x}\pm$ s)

Items	Observation group(n=44)		Control group(n=44)	
	Before treatment	After treatment	Before treatment	After treatment
IL-6(ng/L)	128.48± 12.04	52.45± 5.21*#	129.01± 12.11	87.23± 8.04*
MMP-9(ng/mL)	90.28± 9.12	75.34± 8.24*#	90.31± 9.08	84.32± 8.76*
S100B(ng/mL)	0.78± 0.12	0.24± 0.05*#	0.79± 0.11	0.57± 0.09*

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

2.4 两组不良反应发生情况的比较

在所有患者用药期间均未发生药物不良反应,也未再次出现脑出血。

3 讨论

高血压脑出血具有发病急、病情重、致残率高、死亡率高的特点[6]。在发生高血压脑出血时,血液经颅内血管侵袭至脑实质内后,不仅会给正常脑组织带来压迫性损伤,导致正常脑组织神经细胞缺氧、缺血,使神经细胞面临凋亡、水肿的局面,而且颅内血管会因为血性脑脊液刺激性作用使得脑血管痉挛,进而加重脑灌注不足,进一步扩大脑组织缺氧范围,发生恶性循环[7-9]。因此,使用神经生长因子治疗高血压脑出血患者可抑制神经元凋亡,有利于神经细胞恢复,使受损的神经功能得到重建[10]。

神经生长因子所提取的促使神经损伤修复的成分主要来自于小鼠颌下腺,动物试验表明神经生长因子能增强神经 - 肌肉动作电位幅度,减少神经 - 肌肉动作电位潜伏时间,有利于肢体运动功能障碍的恢复,表明神经生长因子能促使受损神经的修复[11,12]。在现代医学看来,脑内小动脉瘤破裂和脑内小动脉的玻璃样变性会导致高血压脑出血,在出血中风患者中的血液流变性呈现出聚、凝、浓、黏的特点,而活血化瘀要能有效调节血液流变学指标和凝血机制[13]。气属于血之帅,气行则血行,而益气活血能发挥活血化瘀的作用。脑心通胶囊主要是由牛膝、桂枝、川芎、当归、丹参、葛根、赤芍、红花、乳香、三七、水蛭、地龙、全蝎、黄芪组合而成的中药制剂,实现气行则血行的目的,能降低血小板黏附率、外周阻力,扩张小动脉,改善患者血压状况[14]。牛膝、桂枝具有通经络、遂瘀血、温经通脉的作用;赤芍、红花、丹参、川芎、当归属于活血化瘀药物,可降低血液黏滞度、抑制血小板聚集;全蝎、地龙、水蛭能发挥活血、镇痉、通络的作用。在上述诸多药物作用下,脑心通胶囊经益气活血化瘀功能,使得患者的血液凝、聚、黏、浓状态及微循环障碍得到改善[15]。本研究中通过对高血压脑出血患者予以脑心通胶囊联合神经生长因子治疗后,发现总有效率显著高于单纯神经生长因子治疗者,并且患者的 GCS、GOS 评分也得到显著性降低,提示脑心通胶囊联合神经生长因子在治疗高血压脑出血中能发挥明显的优势。究其原因主要是因为脑心通胶囊能改善患者微循环状态,有利于神经功能的恢复,进而改善患者预后。此外,在所有患者用药期间均未发生药物不良反应,提示药物的安全性较高。

高血压脑出血在高血压患者中属于较为严重的一种并发症,会给患者脑部带来严重不良影响,相关的神经功能因子会出现异常波动,在反映患者神经功能受损情况时,常常将 IL-6、MMP-9、S100B 血清因子视为重要且快速的反映指标[16,17]。IL-6 的产生来自于纤维细胞、单核巨噬细胞、B 淋巴细胞、T 淋巴细胞,生物学功能具有多重性,在机体多种组织细胞功能调节、分化和生长中发挥着参与性作用,对炎症和免疫反应均具有重要作用[18]。S100B 作为钙结合蛋白,在中枢神经系统中广泛分布,具有脑特异性,在脑栓塞、脑中风、脑损伤中等均可发现 S100B 指标明显升高,在监测中枢性神经系统损伤中常常将血清 S100B 蛋白视为敏感的指标,有助于评价脑组织缺氧、缺血状态及患者预后[19]。目前,在评估脑出血患者预后中,常常将其视为动态观察指标[20]。本研究结果显示予以脑心通胶囊联合神经生长因子治疗高血压脑出血患者后,患者血清 IL-6、MMP-9、S100B 水平显著降低,且降低的效果优于单纯神经生长因子治疗者,提示在两种药物联合治疗下,更能有效抑制神经炎性反应,能保护出血性脑损伤的脑功能。

总之,脑心通胶囊联合神经生长因子治疗高血压脑出血能有效降低患者血清 IL-6、MMP-9、S100B 水平,临床疗效良好,安全性高。

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(上接第 4931 页)

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