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脑血疏口服液联合依达拉奉对高血压脑出血的治疗效果及对血清 IL-6，IL-1β，MMP-9 的影响 *

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摘要 目的： 研究脑血疏口服液联合依达拉奉对高血压脑出血的治疗效果及对血清白介素 -6 (IL-6)、IL-1β、基质金属蛋白酶 -9 (MMP-9)的影响。**方法：**选取 2014 年 10 月至 2016 年 9 月我院收治的 102 例高血压脑出血患者，根据入院顺序分为观察组和对照组，51 例每组。对照组使用常规治疗，观察组在此基础上采取脑血疏口服液联合依达拉奉完成治疗。比较两组患者临床疗效，神经功能评分、血肿周围水肿量、血肿量，血清 IL-6、IL-1β、MMP-9 水平。**结果：**治疗后，观察组临床总有效率显著高于对照组[94.12%(48/51)比 78.43%(40/51)](P<0.05)；神经功能评分、血肿量、周围水肿量显著低于对照组[(11.04± 1.21)分、(8.65± 0.54)mL、(5.87± 0.54)mL 比(19.87± 1.76)分、(13.56± 1.23)mL、(9.65± 0.92)mL](P<0.05)；血清 IL-6、IL-1β、MMP-9 水平低于对照组[(8.98± 0.87)ng/mL、(12.34± 1.21)ng/L、(74.21± 8.42)ng/L 比(11.21± 1.02)ng/mL、(23.87± 2.37)ng/L、(92.17± 9.86)ng/L](P<0.05)。两组患者不良反应的发生率比较差异无统计学意义(P>0.05)。**结论：**脑血疏口服液联合依达拉奉治疗高血压脑出血的临床疗效明显优于常规治疗，可能与其有效降低患者血清 IL-6、IL-1β、MMP-9 水平有关。

关键词：脑血疏口服液；依达拉奉；高血压；脑出血

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Effects of Cerebral Hemorrhagic Oral Liquid Combined with Edaravone on Hypertensive Cerebral Hemorrhage and Serum IL-6, IL-1β and MMP-9 Levels*

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ABSTRACT Objective: To study the effects of cerebral hemorrhagic oral liquid combined with edaravone on the hypertensive cerebral hemorrhage and the serum Interleukin-6 (IL-6), IL-1β, matrix metalloproteinase-9 (MMP-9) levels. **Methods:** 102 patients with hypertensive intracerebral hemorrhage admitted in our hospital from October 2014 to September 2016 were selected and divided into the observation group and the control group according to the order of admission. The control group was treated with conventional therapy, while the observation group was treated with cerebral hemorrhagic oral solution combined with edaravone on the basis of control group. The clinical efficacy, neurological score, hematoma edema, hematoma volume, serum IL-6, IL-1β and MMP-9 levels were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group [94.12% (48/51) vs. 78.43% (40/51)] (P<0.05). The neurological function score, hematoma volume and edema of observation group were significantly lower than those of the control group [(11.04± 1.21) points, (8.65± 0.54) mL, (5.87± 0.54) mL vs. (19.87± 1.76) points, (13.56± 1.23) mL, (9.65± 0.92) mL](P<0.05). The levels of serum IL-6, IL-1β and MMP-9 of observation group were lower than those of the control group [(8.98± 0.87) ng/mL, (12.34± 1.21) ng/L, (74.21± 8.42)ng/L vs. (11.21± 1.02)ng/mL, (23.87± 2.37) ng/L, (92.17± 9.86) ng/L] (P<0.05). There was no significant difference in the incidence of adverse reaction between the two groups (P>0.05). **Conclusion:** Cerebrospinal fluid combined with edaravone was more effective in the treatment of hypertensive intracerebral hemorrhage than the conventional treatment, which might be related to the reduce of serum IL-6, IL-1β and MMP-9 levels.

Key words: Cerebral hemorrhagic oral solution; Edaravone; Hypertension; Cerebral hemorrhage

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前言

高血压脑出血作为脑血管疾病中的一种具有较高的致残率和病死率。由于患者受到长时间的脑动脉硬化及高血压影响,脑内小动脉出现病理性改变,以至于破裂出血[1]。高血压脑出血的主要临床症状表现为偏瘫、意识障碍、失语、呕吐、头痛等[2]。目前,内科治疗高血压脑出血多以保守疗法为主,但临床疗效不甚理想[3]。依达拉奉作为一种新型强效的羟自由基清除剂,对缺血性脑血管疾病具有良好的临床疗效。脑血疏口服液具有化瘀、活血、益气的功能。血清白细胞介素 -6(IL-6)和基质金属蛋白酶 -9(MMP-9)是水肿及脑出血过程中较为常见的一种敏感检测指标。为给临床在治疗高血压脑出血提供更多可借鉴之处,本研究主要探讨了脑血疏口服液联合依达拉奉对高血压脑出血的治疗效果及对血清 IL-6、IL-1β、MMP-9 水平的的影响。

1 资料与方法

1.1 临床资料

将 2014 年 10 月至 2016 年 9 月我院收治的高血压脑出血患者 102 例纳入本次研究中。纳入标准:① 所有患者均经头颅 CT 检查;② 患者均伴有高血压病史;③ 发病后未开展过开颅或微创等外科手术;④ 发病时间均是在 3 h 内。排除标准:① 肾、肝、肺、心功能不全者;② 中重度昏迷者;③ 生命体征紊乱者。本次研究已取得我院伦理委员会批准, 及得到患者及家属同意。根据患者入院顺序划分为观察组和对照组,51 例每组。观察组中,男性 24 例,女性 27 例;年龄为 38~78 岁,平均(54.87± 4.86)岁;出血量为 4~37 mL,平均(21.21± 4.25)mL;出血部位:小脑叶 7 例,脑干 5 例,脑叶 13 例,基底核区 26 例;高血脂合并者 27 例,糖尿病合并者 17 例。对照组中,男性 26 例,女性 25 例;年龄为 40~79 岁,平均(55.02± 4.92)岁;出血量为 5~42 mL,平均(21.28± 4.31)mL;出血部位:小脑叶 8 例,脑干 6 例,脑叶 12 例,基底核区 25 例;高血脂合并者 24 例,糖尿病合并者 19 例。两组患者年龄、性别、出血量等方面比较差异均无明显统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组按照出血量的不同使用不同剂量的脱水药,根据患者病情使用降血糖药、降血脂药、降血压药,控制感染,防止消化道出血等并发症的发生。观察组在对照组治疗基础上将 100 mL 0.9%的氯化钠注射液和依达拉奉(生产厂家:吉林省辉南长龙生化药业股份有限责任公司,规格:20 mL:30 mg,生产批号:20080592)10 mL 混合后,采取静脉滴注的方式给药,在半个小时内滴完,2 次 / 天,发病 1 天后服用脑血疏口服液(生产厂家:山东沃华医药科技股份有限公司,规格:10 mL/ 支,生产批号:20070059),10 mL/ 次,3 次 / 天,所有患者均以 2 周为一个治疗疗程。

1.3 观察指标

1.3.1 临床疗效评价 通过神经功能缺损评分对两组患者的临床疗效进行评价,治疗后,病残程度为 0 级,NIHSS 评分减少程度为 90%~100%则为基本痊愈;治疗后,病残程度为 1~3 级,NIHSS 评分减少程度为 46%~89%则为显著好转; 治疗后,NIHSS 评分减少程度为 18%~45%则为好转;治疗后,NIHSS 评分减少程度 <18%则为无效[4]。总有效 = 基本痊愈 + 显著好转 + 好转。

1.3.2 神经功能评分、血肿周围水肿量、血肿量分析 比较两组患者治疗前后神经功能评分、血肿周围水肿量、血肿量,使用《美国国立卫生研究所卒中量表》[5]评价神经功能评分,根据多田氏公式计算血肿周围水肿量和血肿量。

1.3.3 血清 IL-6、IL-1β、MMP-9 水平分析 于治疗前后抽取两组患者 5mL 的空腹静脉血,提取上清液后放置在 -50℃低温箱中待测,使用酶联免疫吸附法检测血清 IL-6、IL-1β、MMP-9 水平,由北京中杉金桥公司提供试剂盒,IL-1β 使用电化学发光法进行检测,由北京普尔伟业生物科技公司提供试剂盒,均根据说明书进行严格操作。

1.4 统计学处理

选取 SPSS11.5 软件包对本次实验数据予以处理,用($\bar{x}$± s)表示计量资料进行,进行 t 检验,计数资料以[n(%)]表示,采用 x^2 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比较

治疗后,观察组总有效率显著高于对照组[94.12%(48/51)比 78.43%(40/51)](P<0.05),见表 1。

表 1 两组患者临床疗效分析[例(%)]

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

Groups	Case	Curement	Significant improvement	Improvement	Invalid	Total effective
Observation group	51	24(47.06)	16(31.37)	8(15.69)	3(5.88)	48(94.12)*
Control group	51	17(33.33)	6(11.76)	17(33.33)	11(21.57)	40(78.43)

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

2.2 两组治疗前后神经功能评分、血肿量、周围水肿量的比较

治疗前,两组患者的神经功能评分、血肿量、周围水肿量比较差异无统计学意义(P>0.05);治疗后,两组患者的神经功能评分、血肿量、周围水肿量均较治疗前显著降低(P<0.05),和对照组相比,观察组的神经功能评分、血肿量、周围水肿量较低(P<0.05),见表 2。

2.3 两组治疗前后血清 IL-6、IL-1β、MMP-9 水平的比较

治疗前,两组患者血清 IL-6、IL-1β、MMP-9 水平比较差异无统计学意义 (P>0.05); 治疗后, 两组患者患者血清 IL-6、IL-1β、MMP-9 水平均较治疗前显著降低(P<0.05),与对照组相比,观察组的血清 IL-6、IL-1β、MMP-9 水平较低(P<0.05),见表3。

表 2 两组治疗前后神经功能评分、血肿量、周围水肿量的比较($\bar{x}\pm s$)

Table 2 Comparison of the neurological function score, hematoma volume, amount of edema around between two groups before and after treatment($\bar{x}\pm s$)

Items	Observation group(n=51)		Control group(n=51)	
	Before treatment	After treatment	Before treatment	After treatment
Neurological function score(points)	22.02± 2.31	11.04± 1.21*#	22.05± 2.28	19.87± 1.76*
Hematoma volume(mL)	25.21± 2.43	8.65± 0.54*#	25.25± 2.43	13.56± 1.23*
The amount of edema around(mL)	12.32± 1.21	5.87± 0.54*#	12.35± 1.24	9.65± 0.92*

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

表 3 两种治疗前后血清 IL-6、IL-1β、MMP-9 水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the of serum IL-6, IL-1β, MMP-9 levels between two groups before and after treatment($\bar{x}\pm s$)

Items	Observation group(n=51)		Control group(n=51)	
	Before treatment	After treatment	Before treatment	After treatment
IL-6(ng/mL)	12.02± 1.17	8.98± 0.87*#	12.04± 1.16	11.21± 1.02*
IL-1β(ng/L)	54.11± 5.12	12.34± 1.21*#	54.15± 5.09	23.87± 2.37*
MMP-9(ng/L)	109.21± 12.15	74.21± 8.42*#	108.98± 12.14	92.17± 9.86*

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

2.4 两组患者不良反应发生情况的比较

两组患者不良反应的发生率比较差异无统计学意义(P>0.05),见表 4。

表 4 两组患者不良反应发生情况的比较分析[例(%)]

Table 4 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	Cases	Gastrointestinal bleeding	Lung infection	Rebleeding	Diarrhea	Nausea and vomiting	The total
Observation	51	1(1.96)	3(5.88)	2(3.92)	1(1.96)	1(1.96)	8(15.69)
Control	51	1(1.96)	2(3.92)	1(1.96)	1(1.96)	0(0.00)	5(9.80)

3 讨论

高血压脑出血属于一种神经科较为常见的多发疾病,发病原因主要是脑动脉硬化及高血压等因素致使颅内小动脉出现病理性变化,为脑实质出血的一类[6]。出血后,其出血速度、出血量、出血部位、机体代偿能力等和临床表现的轻重存在着密切关联性[7,8]。依达拉奉作为一种新型强效的羟自由基清除剂,在脂质过氧化反应所导致的神经细胞受损中具有明显的抑制作用,能相应的增强缺血神经元的生存能力,对缺血性脑血管疾病具有良好的临床疗效[9,10]。由于依达拉奉并不会对血流动力学造成影响,因此不会增加扩大脑血肿的危险性。

在中医学看来,脑出血属于离经之血,应遵循"治血者必先祛瘀","离经之血便是瘀"的要领,因此在脑出血中有必要尽早使用活血化瘀重要[11-13]。在中医看来,"气为血之帅",气虚则运血物理,若血行迟滞不畅易形成淤血[14,15]。脑血疏口服液主要根据川穹、大黄、牡丹皮、牛膝、石菖蒲、水蛭、黄芪等组合而成,其中黄芪、水蛭作为君药,黄芪具有补中益气的功能,气旺血行,有利于血肿吸收,水蛭具备破血逐瘀的效果,再加之大黄、石菖蒲、川芎、牛膝、牡丹皮等成分具备活血化瘀、清热凉血的功能,以实现最佳的治疗效果[16-18]。脑血疏口服液具有化瘀、活血、益气的功能。本次研究予以脑血疏口服液联合依达拉奉治疗高血压脑出血患者,其神经功能显著改善,血肿量、周围水肿量明显减少,且临床疗效显著优于常规治疗者。

一旦高血压脑出血患者发生脑出血,脑组织中常常会伴有多种炎症反应发生,此类炎症反应主要由巨噬细胞及中性粒细胞在内的多种炎性细胞浸润[19,20]。脑出血患者因血红蛋白、凝血酶及其分解产物等损伤病灶邻近组织[21,22]。主要是因为脑出血中一旦激活血液成分后,会导致 IL-1、IL-6 等细胞因子释放。体内会因为不同炎性细胞因子含量的上升,会在脑出血中发挥着一起参与的作用,发生继发性脑组织损伤和脑水肿等一系列病理生理过程[23,24]。相关研究者指出脑组织一旦受到损伤后,小胶质细胞或星形胶质细胞等一系列的神经系统细胞会释放出大量的 IL-6,也会因为白细胞数量的增加,进一步升高 IL-6 水平[25]。在高血压脑出血中,机体的补体系统会过度激活,介导白细胞活化和浸润,进而释放出大量的 IL-1β 等炎性细胞因子,出现组织水肿[26,27]。MMP-9 也被称之为明胶酶 B,于正常脑组织中表达较低,一旦发生脑出血后,血肿周围组织会因为炎性因子浸润及缺血缺氧等作用进一步合成 MMP-9[28,29]。相关研究显示出血性脑损伤、缺血和 MMP-9 的表达存在着密切关联性,主要是因为缺血再灌注后炎症反应、脑水肿、血脑屏障开放等因素有关[30]。本研究结果显示脑血疏口服液联合依达拉奉治疗的高血压脑出血患者血清 IL-6、IL-1β、MMP-9 水平治疗后均显著性降低,且效果优于常规治疗者,提示脑血疏口服液和依达拉奉联合治疗能有效抑制 IL-6、IL-1β、MMP-9 等炎性因子水平。

总之,脑血疏口服液联合依达拉奉治疗高血压脑出血的临床疗效明显优于常规治疗,可能与其有效降低患者血清 IL-6、IL-1β、MMP-9 水平有关。

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