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高压氧联合神经节苷脂对高血压脑出血患者术后的影响 *

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摘要 目的: 分析高压氧联合神经节苷脂对高血压脑出血患者微创血肿清除术后的临床疗效。方法: 选择 2012 年 1 月 -2016 年 10 月我院收治的高血压脑出血患者 100 例, 根据随机数字表法分成观察组、对照组, 每组各 50 例。所有患者均先行微创血肿清除术, 对照组患者术后 24 h 内确定体征平稳, 病情稳定后给予高压氧治疗, 观察组在对照组治疗方法的基础之上加用神经节苷脂。比较两组患者的临床疗效、治疗前后神经功能缺损评分(NIHSS)、脑水肿体积、血清基质金属蛋白酶-9(MMP-9)、S100β 蛋白及神经生长因子 (NGF) 的水平变化及术后 3 个月时的日常生活活动能力。结果: 治疗后, 观察组的基本痊愈率显著高于对照组 ($P<0.05$), 两组 NIHSS 评分都较治疗前显著降低, 且观察组 NIHSS 评分显著低于对照组 (P 均 <0.05)。两组手术后第 7 d、14 d 及 28 d 的脑水肿体积均显著低于治疗前 ($P<0.05$), 且观察组各时间点的脑水肿体积均显著低于对照组 ($P<0.05$)。两组血清 MMP-9、S100β 均较治疗前降低 ($P<0.05$), NGF 较治疗前升高 ($P<0.05$), 且观察组治疗后的血清 MMP-9、S100β 水平显著低于、血清 NGF 水平显著高于对照组 ($P<0.05$)。观察组患者术后 3 个月时的日常生活活动能力总良好率显著高于对照组 ($P<0.05$)。结论: 高压氧联合神经节苷脂辅助微创血肿清除术治疗高血压脑出血临床疗效显著, 有利于改善患者预后。

关键词: 高血压; 脑出血; 微创血肿清除术; 高压氧; 神经节苷脂

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Effect of Hyperbaric Oxygenation Combined with Ganglioside on the Hypertensive Cerebral Hemorrhage Patients with Microinvasive Evacuation of Hematoma*

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ABSTRACT Objective: To investigate the effect of hyperbaric oxygenation combined with ganglioside on the hypertensive cerebral hemorrhage patients with microinvasive evacuation of hematoma. **Methods:** 100 cases of hypertensive cerebral hemorrhage patients with microinvasive evacuation of hematoma in our hospital from January 2012 to October 2016 were divided into the observation group and the control group, 50 cases in each group. Patients in the control group were treated with hyperbaric oxygenation after microinvasive evacuation of hematoma, and the observation group were treated with hyperbaric oxygenation combined with ganglioside. The clinical effect, neurological function deficits scale (NIHSS), edema volume in brain, serum levels of MMP-9, S100β, NGF, and the ability of daily life activities at three months after operation were compared between two groups. **Results:** The recovered rate of observation group was significantly higher than that of the control group ($P<0.05$). After treatment, the NIHSS scores, edema volume, serum levels of MMP-9, S100β of both groups were significantly lower than those before treatment ($P<0.05$), which were significantly lower in the observation group than those in the control group ($P<0.05$), and the serum levels of NGF in both groups were significantly higher than those before treatment ($P<0.05$), which was significantly higher in the observation group than that in the control group ($P<0.05$). It was found during the follow up that the excellent rate of ability of daily life of observation group was significantly higher than that of the control group ($P<0.05$). **Conclusions:** Hyperbaric oxygenation combined with ganglioside had remarkably efficacy to treat cerebral hemorrhage patients after microinvasive evacuation of hematoma, it was advantageous for improving the prognosis of patients.

Key words: Hypertension; Cerebral hemorrhage; Microinvasive evacuation of hematoma; Hyperbaric oxygenation; Ganglioside

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前言

高血压脑出血是指由高血压引起的脑内血管破裂性出血,

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具有起病急、发展迅速、破坏性强的特点^[1,2]。据统计,9%-27%的脑卒中患者由脑出血引起,而其中45%脑出血患者由高血压引起^[3,4]。自上世纪60年代开始,微创手术逐渐成为治疗高血压脑出血的重要手段,可及时有效清除患者血肿,解除血肿对周围神经组织的压迫,进而有利于减轻炎症反应、脑水肿、脑组织缺血缺氧引起的脑二次损伤,且创伤小,可促进患者恢复。对于中等量以上出血患者,微创治疗的疗效要显著优于保守治疗^[5,6],但手术后患者不可避免的存在一定程度的脑神经损伤,严重影响患者的预后和生活质量^[7,9]。近年来研究显示高血压脑出血患者微创血肿清除术后联合高压氧有助于患者预后和减少致残率^[10,11]。

神经节苷脂是一种新型中枢神经细胞保护和修复剂,对神经再生有重大促进作用^[12,13]。本院在采用微创血肿清除术后联合高压氧治疗高血压脑出血时加用神经节苷脂,以降低术后患者的脑神经损伤,促进脑神经回复,治疗效果良好,现将结果报道如下。

1 资料与方法

1.1 一般资料

选取2012年1月-2016年10月我院收治的高血压脑出血患者100例,所有患者均经CT检查确诊,且符合我国高血压脑出血的相关诊断标准^[14]。所有患者均有明确高血压史,出血部位均为基底节区,出血量在30 mL以上,均于发病后6-24 h内行微创血肿清除术,术后生命体征平稳;排除合并严重心、肝、肺、肾等脏器功能障碍不能耐受手术者,有脑疝征象者,由脑肿瘤、脑内动脉瘤、凝血机制障碍、动静脉畸形、头部外伤等原因引起的脑出血者,患者发病前即存在意识障碍、精神异常等不能配合临床检查,影响疗效评价者。

根据随机数字表法将患者分成观察组、对照组,每组各50例。观察组中,男性、女性分别有29、21例;年龄35-74岁,平均年龄 (64.51 ± 9.91) 岁,发病距手术时间6-22 h,平均 (12.07 ± 5.64) h,出血量30 mL-55 mL,平均出血量 (43.27 ± 12.09) mL。对照组中,男性27例,女23例;年龄35-75岁,平均年龄 (65.33 ± 9.82) 岁,发病距手术时间6 h-20 h,平均 (12.53 ± 5.22) h,出血量30 mL-55 mL,平均出血量 (41.62 ± 12.57) mL。两组一般资料比较差异无统计学意义($P < 0.05$)。本研究已通过我院伦理委员会审核和批准,所有患者及家属对此研究均知情且已签署知情同意书。

1.2 方法

所有患者均先行微创血肿清除术。方法:术前先进行头颅CT检查,定位穿刺点,以距离颅骨最近点及最大血肿层面的中心部位为穿刺点,选择合适长度的YL-1型颅内血肿穿刺针,所有医疗器械消毒、铺巾,2%利多卡因局部麻醉,常规穿刺,插入穿刺针,进针时注意避开颅内外血管和脑主要功能区,当暗红色的陈旧血液流出之后连接引流管,把针芯退出,小心地抽吸血肿,第一次时先抽吸50%左右,之后0.9%的氯化钠溶液500 ml中加入12500单位的肝素,数次冲洗颅内血肿,置换等量液体,当冲洗液颜色变浅之后连接引流袋,将2-3万U的尿激酶向颅内注入,夹管液化血肿2-3 h后开放引流,每天1次,直至清除血肿90%以上。术后常规抗感染、控制血压等治疗。

对照组:患者术后24 h内,确定体征平稳,病情稳定后给予高压氧治疗,纯氧压力逐渐调至0.20 MPa,升压时间30 min,压力稳定后,患者戴面罩吸纯氧60 min,每吸20 min时休息5 min,降压时间30 min,休息及升降压过程中均摘除患者面罩。每天高压氧治疗1次,10 d为一个疗程,共治疗2个疗程,疗程间间隔3 d-4 d。

观察组:在对照组治疗方法的基础之上加用神经节苷脂(生产厂家:黑龙江哈尔滨医大药业有限公司,国药准字H20060422,规格:20 mg),术后第二天即开始应用,60 mg神经节苷脂溶于250 mL 0.9%的氯化钠溶液中,静脉滴注,1次/d,14 d为一个疗程,共治疗2个疗程。

1.3 观察指标

(1)神经功能缺损评分:使用美国国立卫生研究院卒中量表(NIHSS)对患者治疗前后的神经功能缺损进行评分,0-45分,越高代表受损越严重。(2)临床疗效:根据NIHSS评分评价疗效。基本痊愈:治疗结束时NIHSS评分比治疗前降低91-100%;显效:治疗结束时NIHSS评分比治疗前降低46-90%;有效:NIHSS评分比治疗前降低18-45%;无效:NIHSS评分比治疗前降低或增加小于17%;恶化:NIHSS评分比治疗前增加大于18%或者患者死亡。(3)脑水肿体积:手术前及手术后第7 d、14 d及28 d时,复查头颅CT,计算脑水肿体积。(4)血清相关指标:治疗前及治疗结束后,采集患者外周空腹静脉血5 mL,采用酶联免疫吸附法检测患者血清中基质金属蛋白酶-9(MMP-9)、S100 β 蛋白及神经生长因子(NGF)的水平。(5)日常生活活动:术后3个月时,所有患者来院复诊,对患者进行随访,采用日常生活活动(ADL)量表的Barthel指数(BI)记分法评价患者的日常生活能力,总分0-100分,0-20分为完全依赖,21-45分为重度依赖,46-75分为中度依赖,76-95分及以上为轻度依赖,96-100分为完全独立。

1.4 统计学方法

用SPSS 17.0分析数据,计量资料以 $(\bar{x} \pm s)$ 表示,组间比较采用t检验,计数资料以%表示,组间比较采用卡方检验,以 $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

两组的总有效率比较差异无统计学意义($P > 0.05$),但观察组的基本痊愈率显著高于对照组($P < 0.05$),见表1。

2.2 两组治疗前后NIHSS评分的比较

治疗后,两组的NIHSS评分均较治疗前显著降低($P < 0.05$),且观察组的显著低于对照组($P < 0.05$),见表2。

2.3 两组治疗前后脑水肿体积的比较

治疗前,两组的脑水肿体积比较差异无统计学意义($P > 0.05$)。手术后,两组的脑水肿体积均逐渐缩小,两组手术后第7 d、14 d及28 d的脑水肿体积均显著低于治疗前($P < 0.05$),且观察组各时间点的脑水肿体积均显著低于对照组($P < 0.05$),见表3。

2.4 两组治疗前后血清相关指标水平的比较

治疗前,两组患者血清MMP-9、S100 β 、NGF水平比较差异无统计学意义($P > 0.05$)。治疗后,两组血清MMP-9、S100 β 均

较治疗前降低($P<0.05$),NGF 较治疗前升高($P<0.05$),且观察组 显著高于对照组($P<0.05$),见表 4。
治疗后的血清 MMP-9、S100 β 水平显著低于、血清 NGF 水平

表 1 两组治疗后临床疗效比较[例(%)]

Table 1 Comparison of the clinical effect between two groups after treatment [n(%)]

Groups	Essentially recovered	Excellent	Valid	Invalid	Deterioration	Total effective rate
Observation group (n=50)	25(50.00)*	11(22.00)	8(16.00)	4(8.00)	2(4.00)	44(88.00)
Control group (n=50)	15(30.00)	10(20.00)	16(32.00)	5(10.00)	4(8.00)	41(82.00)

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

表 2 两组治疗前后 NIHSS 评分的比较($\bar{x}\pm s$, 分)

Table 2 Comparison of the NIHSS score between two groups before and after treatment($\bar{x}\pm s$, scores)

Groups	Cases	NIHSS scores	
		Before treatment	After treatment
Observation group	50	35.11 $\pm$ 6.12	11.32 $\pm$ 2.65*
Control group	50	35.07 $\pm$ 6.51	15.35 $\pm$ 3.73

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

表 3 两组治疗前后脑水肿体积的比较($\bar{x}\pm s$, cm³)

Table 3 Comparison of the edema volume of brain between two groups before and after treatment($\bar{x}\pm s$, cm³)

Groups	Cases	Before treatment	At 7 days after operation	At 14 days after operation	At 28 days after operation
Observation group	50	26.07 $\pm$ 4.22	16.32 $\pm$ 4.92* [#]	10.61 $\pm$ 3.52* [#]	2.10 $\pm$ 1.28* [#]
Control group	50	26.51 $\pm$ 4.35	19.55 $\pm$ 5.38*	14.50 $\pm$ 3.82*	5.63 $\pm$ 2.31*

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

表 4 两组治疗前后血清 MMP-9、S100 β 、NGF 水平的比较($\bar{x}\pm s$)

Table 4 Comparison of the serum levels of MMP-9, S100 β , NGF between two groups before and after treatment($\bar{x}\pm s$)

Index	Observation group (n=50)		Control group (n=50)	
	Before treatment	After treatment	Before treatment	After treatment
MMP-9(ng/mL)	125.63 $\pm$ 65.82	15.36 $\pm$ 9.28* [#]	128.33 $\pm$ 72.52	32.32 $\pm$ 15.11*
S100 β (g/mL)	0.30 $\pm$ 0.04	0.18 $\pm$ 0.01* [#]	0.29 $\pm$ 0.03	0.25 $\pm$ 0.02*
NGF(ng/mL)	2.11 $\pm$ 0.62	4.88 $\pm$ 1.05* [#]	2.05 $\pm$ 0.59	3.25 $\pm$ 0.86*

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

2.5 两组治疗前后日常生活活动能力的比较

中总良好率显著高于对照组($P<0.05$),见表 5。

术后随访显示观察组的日常生活活动能力优于对照组,其

表 5 两组治疗前后日常生活活动能力比较[例(%)]

Table 5 Comparison of the activities of daily living between two groups before and after treatment [n(%)]

Groups	Completely dependent	Severe dependent	Moderate dependent	Mild dependent	Completely independent	Good ADL rate
Observation group (n=50)	1	5	11	16	17	44(88.00)*
Control group (n=50)	5	10	10	13	12	35(70.00)

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

3 讨论

随着我国老龄化进程加剧、社会活动节奏加快,高血压脑出血的发病率呈现出上升趋势^[15,16]。高血压脑出血的病理损伤机制主要包括两方面,其一为血肿本身的"占位效应"以及血肿内血红蛋白、凝血酶等物质的释放造成的脑组织原发性损

伤,其二为血肿介导的炎症反应、脑组织水肿、颅内高压、局部脑组织血流不足、血脑屏障损伤等的继发损伤^[17-19]。随着现代医疗技术的进步,微创手术在脑出血中的应用逐渐广泛且技术逐渐娴熟,并且取得了较为理想的治疗效果^[20]。但由于该病发病部位特殊,以及具有起病急、发病迅速的特点,患者术后大多会有一定的脑损伤,故患者术后的神经功能恢复成为目前临床关

注的重点^[21,22]。

高压氧是近年来应用于临床的一种无创治疗手段,众多研究已表明^[23,24]高血压脑出血患者术后早期应用高压氧可有效促进患者神经功能的恢复,减轻继发性脑损伤,其作用机制可能为增加血液氧容量及血氧弥散能力,增加脑组织供养,保护脑细胞内线粒体功能,保护脑细胞和血管内皮细胞的正常生理功能;高压氧下,脑血管收缩,血管内液体外渗减少,利于脑水肿减轻;改善血流动力学指数,进而利于脑血管下降区血液循环的恢复;同时高压氧还可通过降低炎症细胞活性,抑制炎症介质及毒性物质的释放,促进中枢神经细胞的增殖、分化等发挥脑保护作用。

神经节苷脂是神经鞘糖脂的一种,是哺乳动物细胞膜的重要组成部分,大脑皮质的神经元细胞膜中含量丰富,具有保持神经细胞内外离子平衡、维持想立体结构完整性、调节神经细胞膜上酶活性、促进内源性神经生长因子的释放,进而发挥调节神经元的生长、分化和细胞迁移的作用。外源性神经节苷酯通过血脑屏障,聚集于在受损脑区,嵌入细胞膜,替补内源性的神经节苷酯发挥生物学作用^[25]。Lan D B 等^[26]研究显示高血压脑出血患者微创血肿清除术后给予高压氧联合神经节苷酯治疗,可有效改善患者的日常生活能力,促进水中消失,比术后单纯进行高压氧或使用神经节苷脂效果更好。本研究与以上研究结果一致,观察组的基本痊愈率显著比对照组高。两组治疗后的NIHSS 评分均显著降低且观察组 NIHSS 评分显著比对照组低。两组手术后第 7 d、14 d 及 28 d 的脑水肿体积均显著低于治疗前,且观察组各时间点的脑水肿体积均显著低于对照组,术后随访显示观察组患者的日常生活活动能力总良好率显著高于对照组,提示高压氧联合神经节苷脂辅助微创血肿清除术治疗高血压脑出血临床疗效显著。

MMP-9 是基质金属蛋白酶家族的一员,其主要生理作用为作用于细胞外基质中的明胶、IV 型和 V 型胶原、纤维连接蛋白和层粘连蛋白,进而损伤细胞^[27]。在高血压脑出血患者中,MMP-9 会作用于血肿周围血管基底膜细胞基质中相关底物,破坏脑血管基底膜,使其通透性增加,形成水肿或继发脑出血。研究已表明^[28]高血压脑出血患者血清中 MMP-9 水平与脑水肿严重程度密切相关。S100 β 是一种钙离子结合蛋白,有星型胶质细胞分泌,不易透过血脑屏障,正常生理状态下,血清中含量较低,脑组织受损时会被释放入脑脊液,经过血脑屏障进入血清,被广泛应用于脑组织受损后的预后判断^[29]。NGF 为一种蛋白分子,由神经所支配的组织和星型胶质细胞分泌,具有支持突出后神经元的形态和功能完整性的作用,是神经元生长、存活的必须物质^[30]。本研究中治疗后,两组患者血清 MMP-9、S100 β 均显著降低,NGF 显著升高,且观察组治疗后的血清 MMP-9、S100 β 水平显著低于对照组,而血清 NGF 水平显著高于对照组,进一步从分子水平表明高压氧联合神经节苷酯对高血压脑出血患者微创术后的促进预后、减轻脑水肿、促进神经功能恢复的作用,且联合应用的效果要显著优于单用高压氧。

综上所述,高压氧联合神经节苷脂辅助微创血肿清除术治疗高血压脑出血临床疗效显著,有利于改善患者预后。

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