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前列地尔联合尼莫地平对动脉瘤性蛛网膜下腔出血后脑血管痉挛患者血管内皮功能及炎症因子水平的影响*

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摘要 目的:探讨前列地尔联合尼莫地平对动脉瘤性蛛网膜下腔出血(aSAH)后脑血管痉挛(CVS)患者血管内皮功能及炎症因子水平的影响。**方法:**选取 76 例于 2015 年 3 月 ~2017 年 8 月间在中南大学湘雅医院住院治疗的 aSAH 后 CVS 患者为研究对象,按随机数字表法将患者分为对照组(n=38)及观察组(n=38)。对照组在常规治疗基础上采用尼莫地平治疗,观察组在对照组基础上加用前列地尔治疗。比较治疗前后两组患者的大脑前、后、中动脉平均血流速度,观察并比较两组患者血浆降钙素基因相关肽(CGRP)、内皮素 -1(ET-1)水平以及血清血管内皮生长因子(VEGF)、白细胞介素 -8(IL-8)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子 -α(TNF-α)水平的变化情况,评价两组疗效并观察治疗过程中的不良反应发生情况。**结果:**与对照组比较,治疗后观察组大脑前、后、中动脉血流速度均明显降低(P<0.05)。与治疗前比较,治疗后两组患者 CGRP 水平明显升高,与对照组比较,治疗后观察组 CGRP 水平明显升高(P<0.05),而治疗后两组患者 ET-1、VEGF 水平明显下降,且观察组低于对照组(P<0.05)。与治疗前比较,治疗后两组患者 IL-8、hs-CRP、TNF-α 水平均明显下降,且与对照组比较,观察组 IL-8、hs-CRP、TNF-α 水平均降低(P<0.05)。观察组患者治疗的总有效率为 92.11%,明显高于对照组的 73.68%(P<0.05)。观察组总不良反应发生率与对照组比较差异无统计学意义(P>0.05)。**结论:**前列地尔与尼莫地平联合使用治疗 aSAH 后 CVS 能明显改善患者的血管内皮功能,降低炎症因子水平,且未增加用药的不良反应,治疗效果较好。

关键词:前列地尔;尼莫地平;动脉瘤性;蛛网膜下腔出血;脑血管痉挛

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Effects of Alprostadil and Nimodipine on Vascular Endothelial Function and Inflammatory Factors in Patients with Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage*

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ABSTRACT Objective: To investigate the effects of alprostadil and nimodipine on vascular endothelial function and inflammatory factors in patients with aneurysmal subarachnoid hemorrhage (aSAH) after cerebral vasospasm (CVS). **Methods:** 76 cases of aSAH after CVS patients who were hospitalized in Xiangya Hospital of Central South University from March 2015 to August 2017 were selected as the research subjects, the patients were divided into the control group (n=38) and the observation group (n=38) according to the random number table method. The control group was treated with nimodipine on the basis of routine treatment, the observation group was treated with alprostadil on the basis of the control group. The average velocity of blood flow in the anterior, posterior and middle cerebral arteries of the two groups before and after treatment were compared. The changes of plasma calcitonin gene related peptide (CGRP),endothelin-1 (ET-1) and the level of serum vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8), high sensitive C reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) were observed and compared, the efficacy of two groups were evaluated and the occurrence of adverse reactions in the treatment were observed. **Results:** Compared with the control group, the blood flow velocity of anterior cerebral artery, posterior cerebral artery and middle cerebral artery in the observation group after treatment were decreased significantly(P<0.05). Compared with those before treatment, the level of CGRP in the two groups after treatment was significantly increased, compared with the control group, the level of CGRP in the observation group after treatment was significantly increased (P<0.05). After treatment, the levels of ET-1 and VEGF in the two groups were significantly decreased, and the observation group was lower than that in the control group (P<0.05). Compared with those before treatment, the levels of IL-8, hs-CRP and TNF-α in the two groups after treatment were significantly decreased, and compared with the control group, the levels of IL-8, hs-CRP and TNF-α in the observation group were all decreased(P<0.05). The total effective rate of the patients in the observation group was 92.11%, which was significantly higher than 73.68%

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of the control group (P<0.05). There was no significant difference in the incidence of total adverse reactions between the obser- vation group and the control group (P>0.05). **Conclusion:** The combination of alprostadil and nimodipine in the treatment of aSAH afetr CVS can significantly improve the vascular endothelial function and reduce the levels of inflammatory factors, and the adverse reaction of the drug is not increased, the treatment effect is better.

Key words: Alprostadil; Nimodipine; Aneurysmal; Subarachnoid hemorrhage; Cerebral vasospasm

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前言

动脉瘤性蛛网膜下腔出血（aneurysmal subarachnoid hemorrhage,aSAH)是指因动脉瘤破裂,血液流入蛛网膜下腔而发生的一组临床综合征,其具有起病急、病情重、并发症多等特点[1,2]。脑血管痉挛(cerebral vasospasm,CVS)是 aSAH 的一种常见且严重的并发症,发生率可达 70%左右,若未得到及时有效地处理，将进一步引发迟发性缺血性脑功能障碍或局部脑缺血,甚至导致脑梗死,对患者的生命安全造成严重威胁[3,4]。aSAH 后 CVS 的发生机制尚不完全明确,但近年来研究认为,其与血管内皮功能障碍、炎症反应等因素存在一定联系 [5,6]。目前对于 aSAH 后 CVS 尚无特异性的治疗方案,因此临床上多在 aSAH 发生之后及时进行治疗，以防止 CVS 及其它严重并发症的发生[7,8]。前列地尔和尼莫地平均为临床上治疗 aSAH 后 CVS 的常用药物,但单药使用效果均不理想。本研究采用前列地尔联合尼莫地平对 aSAH 后 CVS 患者进行治疗，并观察患者血管内皮功能及炎症因子水平的变化情况,以期为临床用药提供数据支持。

1 资料与方法

1.1 一般资料

选取 76 例于 2015 年 3 月 ~2017 年 8 月间在中南大学湘雅医院住院治疗的 aSAH 后 CVS 患者作为研究对象。纳入标准[9]:(1)所有患者均经头颅 CT 确诊为自发性 aSAH,并经头颅数字减影血管造影确诊为颅内动脉瘤;(2)均为突发起病,且发病至就诊时间小于 72 h;(3)术后 14 d 内均出现头痛、意识和认知功能障碍等 CVS 症状;(4)Hunt-Hess 分级≤ Ⅲ级;(5)患者家属对研究知情并签署同意书。排除标准:(1)重症肌无力、强直性肌营养不良者;(2)低血压(血压低于 90/60 mmHg)者;(3)合并恶性肿瘤者;(4)心、肺、肾等脏器功能不全者;(5)合并血液疾病、免疫系统疾病者。本研究已经我院伦理委员会批准通过。将所有患者按随机数字表法分为对照组(n=38)及观察组(n=38)。两组患者性别、年龄、发病到入院时间、Hunt-Hess 分级等一般资料列于表 1，经统计分析结果显示，差异均无统计学意义(P>0.05)。

表 1 两组患者一般资料比较

Table 1 Comparison of general information of patients between two groups

Groups	n	Gender(male/female)	Age (years old)	Onset to admission time(h)	Hunt-Hess grade (I/II/III)
Control group	38	22/16	55.68± 7.42	7.43± 3.58	10/21/7
Observation group	38	20/18	54.93± 7.81	7.19± 3.40	9/21/8
t/x^2	-	0.213	0.429	0.300	0.126
P	-	0.645	0.669	0.765	0.791

1.2 治疗方法

所有患者在行颅内动脉瘤栓塞夹闭术后,进行保持呼吸道通畅、调控血压、脱水降颅压、纠正休克、止血、预防感染、预防并发症等常规治疗。对照组患者给予尼莫地平（国药准字:H20030306,生产厂家:济川药业集团有限公司,规格:10 mg/50 mL)50 mL,加入 150 mL 0.9%NaCl 中静脉滴注,1 次 /d,连续治疗 14 d。在服用尼莫地平的基础上,观察组患者加用前列地尔(国药准字:H20084565,生产厂家:哈药集团生物工程有限公司,规格:10 μg/2 mL)治疗,剂量为 10 μg,加入 10 mL 0.9% NaCl 中缓慢静注,1 次 /d,连续治疗 14 d。

1.3 观察指标及评价标准

所有患者均于治疗前及治疗 14 d 后进行彩色多普勒超声检查,测定大脑前、后、中动脉平均血流速度。分别于治疗前及治疗 14 d 后的清晨抽取患者空腹状态下的肘静脉血 6 mL,其中 3 mL注入已加肝素抗凝的试管中,以 3000 rpm 速率离心 10 min 并分离血浆,-80℃ 下保存待测;另外 3 mL注入未加肝素抗凝的试管中，以 3000 rpm 离心 10 min 并分离血清,-80℃ 下保存待测。采用放射免疫法(试剂盒购自深圳晶美生物工程有限公司)检测血浆降钙素基因相关肽(CGRP)、内皮素 -1(ET-1)水平,操作均严格按照说明书进行。采用酶联免疫吸附法(试剂盒购自上海江莱生物科技有限公司）测定血清血管内皮生长因子(VEGF)、白细胞介素 -8(IL-8)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子 -α(TNF-α)水平,操作均严格按照说明书进行。

治疗结束后对所有患者的治疗效果进行评价。评价标准[10]:无效:患者病情无明显改善,甚至加重;有效:患者的血流速度和神经功能缓慢恢复,临床症状有所减轻;显效:患者血流速度恢复正常、神经功能得到明显的改善,临床症状、体征基本消失。总有效率 = 显效率 + 有效率。对治疗过程中两组患者出现

的不良反应情况进行观察并比较。

1.4 统计学方法

采用 SPSS22.0 软件处理分析本次研究的所有数据。其中计数资料以“例”、“率”表示，其比较采用 x^2 检验。计量资料经检验均符合正态分布，以($\bar{x}\pm s$)表示，采用 t 检验。将α=0.05 设置为检验标准。

2 结果

2.1 两组患者大脑动脉血流速度比较

治疗前，两组患者大脑前、后、中动脉血流速度比较差异均无统计学意义(P>0.05)。治疗后，两组患者大脑前、后、中动脉血流速度均明显降低，且观察组大脑前、后、中动脉血流速度均明显低于对照组(P<0.05)。见表 2。

表 2 两组患者大脑动脉血流速度比较($\bar{x}\pm s$，cm/s)

Table 2 Comparison of cerebral artery blood flow velocity between two groups($\bar{x}\pm s$, cm/s)

Groups	n	Anterior cerebral artery		Posterior cerebral artery		Middle cerebral artery	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	38	113.26± 7.43	96.53± 6.98*	76.95± 5.63	67.35± 4.03*	104.35± 8.13	97.21± 7.84*
Observation group	38	112.89± 7.91	73.34± 4.11*	77.27± 5.51	53.81± 1.74*	104.88± 7.96	83.31± 4.40*
t	-	0.210	17.648	0.250	19.015	0.287	9.531
P	-	0.834	0.000	0.803	0.000	0.775	0.000

Note: compared with before treatment, *P<0.05.

2.2 两组患者血管内皮功能相关指标比较

治疗前，两组患者血管内皮功能相关指标经统计分析差异均无统计学意义（P>0.05）。与治疗前比较，治疗后两组患者 CGRP 水平明显上升，与对照组比较，治疗后观察组 CGRP 水平明显升高(P<0.05)；而治疗后两组患者 ET-1、VEGF 水平明显下降，且与对照组比较，治疗后观察组 ET-1、VEGF 水平明显降低(P<0.05)。见表 3。

表 3 两组患者血管内皮功能相关指标比较($\bar{x}\pm s$)

Table 3 Comparison of vascular endothelial function indexes between two groups($\bar{x}\pm s$)

Groups	n	CGRP(pg/mL)		ET-1(pg/mL)		VEGF(ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	38	38.03± 4.83	46.91± 6.42*	134.89± 11.33	92.69± 12.43*	216.84± 22.91	146.89± 16.27*
Observation group	38	38.56± 5.12	56.14± 7.72*	135.26± 12.27	73.10± 11.92*	215.19± 23.88	122.54± 29.51*
t	-	0.464	5.667	0.137	7.012	0.307	4.454
P	-	0.644	0.000	0.892	0.000	0.759	0.000

Note:compared with before treatment, *P<0.05.

2.3 两组患者炎性因子水平比较

治疗前，两组患者各炎性因子水平经统计分析差异均无统计学意义（P>0.05）。与治疗前比较，治疗后两组患者 IL-8、hs-CRP、TNF-α 水平均明显下降，且与对照组比较，治疗后观察组各指标水平均降低(P<0.05)。见表 4。

表 4 两组患者炎性因子水平比较($\bar{x}\pm s$，ng/mL)

Table 4 Comparison of inflammatory factors in two groups of patients($\bar{x}\pm s$, ng/mL)

Groups	n	IL-8		hs-CRP		TNF-α	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	38	3.82± 0.43	2.16± 0.33*	251.37± 28.62	207.81± 24.75*	0.53± 0.14	0.34± 0.09*
Observation group	38	3.77± 0.41	1.45± 0.29*	252.94± 29.31	188.72± 22.49*	0.51± 0.12	0.26± 0.11*
t	-	0.519	9.963	0.236	3.519	0.669	3.470
P	-	0.605	0.000	0.814	0.001	0.506	0.001

Note:compared with before treatment, *P<0.05.

2.4 两组患者的治疗效果比较

与对照组比较，观察组患者治疗的总有效率明显升高(P<0.05)。见表 5。

表 5 两组患者的治疗效果比较[n(%)]

Table 5 Comparison of therapeutic effects of patients between two groups [n(%)]

Groups	n	Excellence	Effective	Invalid	Total effective rate
Control group	38	11(28.94)	17(44.74)	10(26.32)	28(73.68)
Observation group	38	13(34.21)	22(57.90)	3(7.89)	35(92.11)
x^2	-				4.547
P	-				0.033

2.5 两组患者不良反应发生情况比较

对照组共出现胃肠道反应 4 例、血压下降 4 例、皮疹 1 例、头晕头痛 2 例;观察组共出现胃肠道反应 3 例、血压下降 4 例、皮疹 1 例、头晕头痛 2 例。观察组总不良反应发生率为 26.32%(10/38),与对照组的 28.95%(11/38)比较,差异无统计学意义(x^2=0.066,P=0.798)。

3 讨论

CVS 可通过头颅 CT、彩色多普勒超声、核磁共振等手段发现,该病患者主要表现为因局部或弥漫性的血管损伤而导致的暂时性脑血管直径缩小或颅底血管动脉壁平滑肌的持续收缩[11,12]。CVS 的发生将引发更为严重的迟发性脑缺血,最终将导致患者神经功能障碍、认知功能障碍,甚至残疾、瘫痪[13,14]。CVS 多发于 aSAH 后两周内,其发病高峰为第 5~10 d,已有大量研究表明,CVS 正是 aSAH 高致死率、致残率最主要的原因之一[15-17]。aSAH 后 CVS 的发生是可以防治的[18-20],临床上常采用药物治疗 CVS,尼莫地平是目前公认的治疗 CVS 的有效药物,但其半衰期较短,导致疗效也较短暂[21],因此,一般采用其与其他药物联合使用以治疗 CVS。

本研究选取动脉瘤破裂急性期(发病至就诊时间小于 72 h)行颅内动脉瘤栓塞夹闭术的 aSAH 患者,治疗 14 d 后发现,联用前列地尔与尼莫地平的患者大脑前、后、中动脉血流速度下降更为明显,说明两药的联合使用对于改善患者脑血流速度效果更佳。前列地尔是一种钙离子通道阻滞剂,具有抑制血小板聚集、活化的作用,同时还可以通过增加环磷腺苷在血管平滑肌细胞内的含量,达到扩张血管的效果[22,23]。尼莫地平同样是一种钙离子通道阻滞剂,其具有很高的是脂溶性,在缓解颅内平滑肌收缩、增加脑动脉血流、选择性保护血管扩张效应以及保护脑组织神经细胞方面均有较好的作用[24-26]。而本研究结果也表明,前列地尔与尼莫地平具有协同作用,与单药比较,其可更为有效地改善 aSAH 后 CVS 患者的脑动脉及其周围组织循环,有利于其周围低密度区的体积以及小血肿的缩小。血管内皮细胞在接受物理、化学刺激后,可通过各种血管活性物质的合成、分泌,发挥调节血管张力、抑制血栓形成和控制血管生长的生物学效应[27]。血管内皮细胞功能受到损伤时,可导致血管异常收缩或痉挛,并可促进血栓的形成,进一步引发缺血性损伤。aSAH 发生后,血管外壁暴露在红细胞裂解产物释放的氧合血红蛋白等成分中,引起包括白细胞的募集、浸润、活化在内的一系列炎症级联反应。血管内皮损伤及炎症反应均是引发 aSAH 后 CVS 的重要原因[28,29]。本研究中,观察组治疗后的血管内皮功能相关指标水平和炎性因子水平均优于治疗前及对照组,进一步说明与单独使用尼莫地平比较,前列地尔与尼莫地平联用对 aSAH 后 CVS 患者的血管内皮功能的保护作用明显更好,且对炎症反应也有更好的调节作用。本研究结果发现,前列地尔与尼莫地平联用,总有效率得到明显提升,而从不良反应情况看,两组患者又无明显的差异,提示前列地尔联合尼莫地平治疗 aSAH 后 CVS 患者具有一定的优越性。张岚[30]的报道也得到了类似的结论,但是张岚的报道中试验组的有效率为 86.96%,低于本研究的 92.11%,且患者不良反应较为严重,推测与所纳入的患者的病情有关。本研究选取 Hunt-Hess 分级≤ Ⅲ级的患者,疗效较为理想,而对病情更为严重的患者,仍需寻找更为有效的治疗方式。

综上所述,前列地尔与尼莫地平联合使用治疗 aSAH 后 CVS 能明显改善患者的血管内皮功能并降低炎症因子水平,且未增加用药的不良反应,治疗效果较好。临床上对于 Hunt-Hess 分级≤ Ⅲ级的 aSAH 后 CVS 患者,可考虑推广使用该治疗方式。

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