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腰大池引流联合法舒地尔治疗动脉瘤性蛛网膜下腔出血的疗效及对血清 sICAM-1、FABP、MCP-1 水平和脑积水形成的影响 *

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摘要 目的: 分析腰大池引流联合法舒地尔治疗动脉瘤性蛛网膜下腔出血的疗效及对血清可溶性细胞间黏附分子-1(sICAM-1)、脂肪酸结合蛋白质(FABP)、核细胞趋化蛋白(MCP-1)水平和脑积水形成的影响。**方法:** 选择我院 2016 年 3 月~2018 年 3 月收治的 112 例动脉瘤性蛛网膜下腔出血患者, 按随机数字表法分为对照组(n=48)和研究组(n=64)。对照组采用腰大池引流治疗, 研究组基于对照组联合法舒地尔治疗。比较两组临床疗效, 治疗前后血清 sICAM-1、FABP、MCP-1 水平、血压、大脑中动脉血流参数水平和神经功能的变化, 脑积水发生率及不良反应发生情况。**结果:** 治疗后, 研究组总有效率显著高于对照组(89.02% vs. 72.91%, $P<0.05$)。两组治疗后血清 sICAM-1、FABP、MCP-1、血压、大脑中动脉血流参数水平和神经功能缺损评分量表(NIHSS)均较治疗前下降, 格拉斯哥昏迷评分(GCS)均较治疗前上升, 研究组以上指标较对照组改变更明显(均 $P<0.05$)。两组不良反应发生情况比较差异无统计学意义($P>0.05$)。**结论:** 腰大池引流联合法舒地尔治疗动脉瘤性蛛网膜下腔出血的疗效明显优于单用腰大池引流治疗, 其可显著降低血清 sICAM-1、FABP、MCP-1 水平, 降低脑积水发生率, 改善患者预后。

关键词: 动脉瘤性蛛网膜下腔出血; 腰大池引流; 法舒地尔; 疗效; 可溶性细胞间黏附分子-1; 脂肪酸结合蛋白质; 核细胞趋化蛋白; 脑积水

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Curative Efficacy of Lumbar Cistern Drainage Combined with Fasudil in the Treatment of Aneurysmal Subarachnoid Hemorrhage and Its Effect on the Serum Levels of sICAM-1, FABP, MCP-1 and Hydrocephalus Formation*

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ABSTRACT Objective: To analyze the curative effect of lumbar cistern drainage combined with fasudil in the treatment of aneurysmal subarachnoid hemorrhage and the effect of serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), fatty acid binding protein (FABP), nuclear chemokine protein (MCP-1) and hydrocephalus. **Methods:** 112 cases of patients with aneurysmal subarachnoid hemorrhage who treated from March 2016 to March 2018 in our hospital, according to random number table method those patients were divided into the control group (n=48) and research group (n=64), the control group was treated with lumbar cistern drainage, the research group was treated with fasudil based on the control group, then clinical curative effect, changes in serum levels of sICAM-1, FABP, MCP-1, blood pressure, blood flow parameters in the middle cerebral artery, and neurological function before and after treatment, and the incidence of hydrocephalus, adverse reactions occur in both group were compared. **Results:** After treatment, total effective rate of the research group was significant higher than that of the control group (89.02% vs. 72.91%, $P<0.05$). The levels of sICAM-1, FABP, MCP-1, blood pressure, blood flow parameters of the middle cerebral artery, and the score scale for neurological impairment (NIHSS) in the two groups all decreased after treatment, and the Glasgow coma score (GCS) increased after treatment. The above indexes in the research group were more significantly changed than those in the control group (all $P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The efficacy of lumbar cistern drainage combined with fasudil in the treatment of aneurysmal subarachnoid hemorrhage is definitely better than that of lumbar cistern drainage alone, which can significantly reduce the levels of sICAM-1, FABP, MCP-1, the incidence of hydrocephalus, and improve the prognosis of patients.

Key words: Aneurysmal subarachnoid hemorrhage; Lumbar cistern drainage; Fasudil; Curative effect; Soluble intercellular

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adhesion molecule-1; Fatty acid binding protein; Nucleocyte chemotactic protein; Hydrocephalus

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前言

蛛网膜下腔出血为神经科的常见急症,是脑表层或者脑底部病变血管破裂,主要是动脉瘤破裂,血液直接流入蛛网膜下腔所致的临床综合征,能够直接破坏中枢神经系统的结构及功能,可引起多种并发症^[1,2]。其中,脑积水是其严重并发症之一,可明显增加患者致残率及病死率,严重危及患者的健康及生命^[3]。腰大池引流术是动脉瘤性蛛网膜下腔出血的微创疗法,可减轻颅内高压状态,降低脑梗死、再出血等严重并发症危险性^[4,5]。但有研究表明^[6]腰大池引流术对部分动脉瘤性蛛网膜下腔出血患者的效果不甚理想。法舒地尔注为新型的钙离子拮抗剂,可有效控制脑卒中缺血、缺氧所致的脑细胞损伤,改善脑部组织循环,但缺乏对作用机制的相关报道^[7]。

动脉瘤性蛛网膜下腔出血的发生机制复杂,有关研究显示^[8]其发生可能与免疫炎症反应有关。可溶性细胞间黏附分子-1(sICAM-1)可诱导白细胞黏附至血管内皮细胞,经内皮屏障转移至组织中,组织受到炎症、缺血缺氧刺激下可激活sICAM-1,从而起到系列生理病理反应。脂肪酸结合蛋白质(FABP)能够调节细胞内脂肪酸浓度,动脉瘤性蛛网膜下腔出血者FABP浓度明显上升^[9]。核细胞趋化蛋白-1(MCP-1)可诱导单核巨噬细胞在动脉壁黏附及浸润,降解动脉壁弹力纤维,促进动脉瘤发生发展,参与脑损伤。本研究主要分析腰大池引流通联合法舒地尔治疗动脉瘤性蛛网膜下腔出血的疗效及对血清sICAM-1、FABP、MCP-1和脑积水形成的影响,结果报道如下。

1 资料与方法

1.1 一般资料

选择我院2016年3月~2018年3月收治的112例动脉瘤性蛛网膜下腔出血患者,纳入标准^[10]:经影像学、脑脊液、脑血管影像学及实验室检查确诊为动脉瘤性蛛网膜下腔出血;世界神经外科联盟分级为II~IV级;发病后48h内入院;无本研究脑脊液置换术及药物禁忌症。排除标准:脑实质出血、颅内血肿;严重代谢性疾病或者内脏疾病;陈旧性颅内血肿、脑梗死、脑血管阻塞或者烟雾病;头颅外伤病史、肿瘤;妊娠或者哺乳阶段。按随机数字表法分为对照组(n=48)和研究组(n=64),对照组男27例,女21例;年龄36~67岁,平均(55.41±9.13)岁;世界神经外科联盟分级:II级16例、III级23例、IV级9例;基底动脉瘤5例,大脑中动脉瘤10例,颈内动脉后交通动脉瘤16例,前交通动脉瘤17例。研究组男28例,女36例(与前面64例不符);年龄35~69岁,平均(56.05±8.74)岁;世界神经外科联盟分级:II级24例、III级30例、IV级10例;基底动脉瘤7例,大脑中动脉瘤15例,颈内动脉后交通动脉瘤23例,前交通动脉瘤19例。两组一般资料比较无统计学差异(P>0.05),具有可比性。

1.2 治疗方法

患者入院后均绝对卧床,稳定情绪,接受止痛、镇静、降颅内压、保持水电解质平衡等治疗,保持大便通畅,避免打喷嚏及

用力咳嗽。患者均采用血管内介入栓塞术治疗,术后第二日复查脱落CT无明显脑肿胀后,对照组采用腰大池引流治疗,指导患者为侧卧位,保持胸、膝屈曲,常规消毒腰3~4或者4~5椎间隙,并实施局部麻醉。取硬膜外穿刺针进行穿刺,待脑脊液外流则进入腰大池,于间隙内放置硬膜外管(约10 cm),待脑脊液顺利流出后接通引流袋,使引流管固定。引流速度保持在5~20 mL/h,每日引流量约为200 mL,通常引流5~10日不等,平均引流4~7日,直至脑脊液红细胞数量降至正常。(更换为术后第二日复查脱落CT无明显脑肿胀后,行腰大池置管引流,通常引流5~10日不等,平均引流4~7日,直至脑脊液红细胞数量降至正常)研究组在对照组基础上联合法舒地尔(天津金耀集团湖北天药药业股份有限公司,2 mL/支,20150329)治疗,将30 mg法舒地尔+100 mL生理盐水在30 min内滴注,每天3次,持续治疗14d。于治疗结束时评估临床疗效,记录不良反应发生情况。

1.3 观察指标

1.3.1 临床疗效 症状及体征全部消失,治疗结束后患者生活能够自理为显效;症状及体征显著改善,伴程度不一的后遗症为有效;症状及体征无明显改变甚至加重为无效。显效率及有效率为总有效率^[10]。

1.3.2 血液指标 于治疗前及治疗结束时采集患者2 mL空腹外周静脉血,常规分离血清,保留上清液在-20℃低温箱中待检。用酶联免疫吸附法检测sICAM-1、FABP、MCP-1水平。

1.3.3 血压及大脑中动脉血流参数测定 于治疗前及治疗结束时上午10点左右进行血压测定,待患者安静休息15分钟后,由专人采用标准电子血压计检测其右臂坐位血压值,连测3次(中间间隔1分钟),取平均值。采用多普勒超声诊断仪测定大脑中动脉血流参数。

1.3.4 神经功能 神经功能缺损评分量表(NIHSS)按照意识水平、凝视、视野、上肢运动、下肢运动、面瘫、感觉等方面评估,分数越高表示神经功能损伤越严重。格拉斯哥昏迷评分(GCS)按照运动反应、言语、睁眼3个方面进行,13~15分即轻度神经功能受损、9~12分即中度神经功能受损、3~8分即重度神经功能受损。

1.4 统计学分析

数据处理选用SPSS18.0软件包,计量资料用($\bar{x} \pm s$)表示,组间比较选用独立样本t检验,计数资料用[(%)表示,组间比较用 χ^2 检验,以P<0.05表示差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后研究组总有效率高于对照组(89.02% vs. 72.91%, P<0.05),见表1。

2.2 两组治疗前后血清sICAM-1、FABP、MCP-1水平比较

治疗前,两组血清血清sICAM-1、FABP、MCP-1水平比较无统计学差异(P>0.05);治疗后,两组血清sICAM-1、FABP、

MCP-1 水平均较治疗前显著下降,且研究组以上指标均显著低于对照组($P<0.05$),见表 2。

表 1 两组临床疗效比较(例%)
Table 1 Comparison the clinical efficacy between two groups[(n)%]

Groups	n	Effective	Effective	Onvalid	Total effective rate
Control group	48	20(41.67)	15(31.25)	13(27.08)	35(72.91)
Research group	64	35(54.68)	22(34.38)	7(10.94)	57(89.06)*

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

表 2 两组治疗前后血清 sICAM-1、FABP、MCP-1 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of serum levels of sICAM-1, FABP, MCP-1 before treatment and after treatment between two groups ($\bar{x}\pm s$)

Groups	n	Time	sICAM-1(ng/mL)	FABP(ng/L)	MCP-1(ng/L)
Control group	48	Before treatment	840.29± 100.28	1071.62± 130.94	215.08± 30.29
		After treatment	499.75± 75.41 [#]	770.80± 98.53 [#]	180.53± 29.01 [#]
Research group	64	Before treatment	832.71± 107.52	1088.49± 126.75	223.62± 25.42
		After treatment	430.82± 60.59**	511.64± 69.06**	158.09± 20.85**

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

2.3 两组治疗前后血压、大脑中动脉血流参数水平比较

治疗前,两组血压、大脑中动脉血流参数水平比较无统计

学差异($P>0.05$);治疗后,两组血压均较治疗前显著下降,大脑中动脉血流参数水平较治疗前明显上升,且研究组以上指标变化幅度较对照组更小($P<0.05$),见表 3。

表 3 两组治疗前后血压、大脑中动脉血流参数水平比较($\bar{x}\pm s$)

Table 3 Comparison of the blood pressure, blood flow parameters in the middle cerebral artery before treatment and after treatment between two groups ($\bar{x}\pm s$)

Group	n	Time	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Middle cerebral artery blood flow parameter level(cm/L)
Control group	48	Before treatment	147.05± 19.05	108.16± 12.17	132.08± 19.04
		After treatment	126.03± 15.41 [#]	87.51± 12.85 [#]	92.15± 13.48 [#]
Research group	64	Before treatment	149.21± 16.33	106.77± 14.03	136.26± 16.53
		After treatment	110.86± 12.05**	83.20± 10.93**	82.17± 11.27**

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

2.4 两组治疗前后神经功能的比较

治疗前,两组神经功能比较无统计学差异($P>0.05$);治

疗后,两组 NIHSS 评分均较治疗前降低,GCS 评分较治疗前均上升,且研究组以上指标变化幅度较对照组更小($P<0.05$),见表 4。

表 4 两组治疗前后神经功能的比较($\bar{x}\pm s$)

Table 4 Comparison of nerve function before treatment and after treatment between two groups ($\bar{x}\pm s$)

Groups	n	Time	NIHSS(points)	GCS(points)
Control group	48	Before treatment	16.68± 2.86	9.95± 1.15
		After treatment	11.61± 1.75 [#]	12.37± 1.96 [#]
Research group	64	Before treatment	17.30± 2.04	9.64± 1.52
		After treatment	9.95± 1.20**	14.85± 1.80**

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

2.5 两组脑积水发生情况比较

治疗后,研究组脑积水发生率低于对照组(7.81%(5/64)和 20.83%(10/48))($P<0.05$)。

2.6 两组不良反应的发生情况比较

两组均有脑血管痉挛、再出血、肺部感染、胃肠道反应发生,研究组脑血管痉挛率低于对照组($P<0.05$),见表 5。

3 讨论

动脉瘤性蛛网膜下腔出血为脑血管疾病的常见类型,发病

表 5 两组不良反应的发生情况比较[例(%)]

Table 5 Comparison the incidence of adverse reactions between two groups [n(%)]

Groups	n	Cerebrovascular	Rebleeding	lung infection	Gastrointestinal reaction	Total adverse reaction rate
Control group	48	6(12.50)	1(2.08)	2(4.17)	1(2.08)	10(20.83)
Research group	64	1(1.56)	2(3.13)	4(6.25)	3(4.68)	12(18.75)

急,症状重,病死率高^[1]。临床资料显示部分动脉瘤性蛛网膜下腔出血患者血液可进入脑室,阻碍脑脊液循环,增加颅内压,对脑干及下丘脑起到压迫及刺激作用,导致高热、循环衰竭等多种症状^[2]。腰大池引流操作简便,引流速度比较均匀缓慢,可控性强,能够避免过度引流,减少脑疝危险性,可通过开放腰大池引流管,建立引流冲洗通道,进而清除脑室内与蛛网膜下腔的有害物质,避免继发性脑部受损^[3]。腰大池引流通过持续引流能够使感染脑脊液排出体外,降低颅内压力,进而刺激脑脊液的分泌,形成冲洗与稀释作用,减少感染所致蛛网膜粘连,避免发生交通性脑积水,减少癫痫及脑膜刺激的发作。且其可动态观察脑脊液状态,利于细菌培养和生化检查的实施,掌握感染控制的状况,进而指导临床用药^[4]。Newton PL 等^[5]研究报道单一腰大池引流难以达到良好的效果,且需反复多次腰穿,有一定的感染可能性。

法舒地尔注射液为 RHO 激酶的抑制物,且为 5- 异喹啉磺酰胺的衍生物,能够增加肌球蛋白的相关酶活性,促进血管扩张,降低内皮细胞张力,缓解脑部组织的微循环,促进脑灌注的改善,提高脑部对缺氧的能力,改善患者预后^[6,17]。此外,法舒地尔可减轻炎症反应,避免神经细胞发生凋亡,利于其再生。动脉瘤性蛛网膜下腔出血可诱导大量钙离子在脑内皮细胞及微血管处聚集,引起脑组织发生缺血缺氧,开放钙离子通道,产生钙离子超出状态,从而诱导继发性的脑水肿、损伤^[18]。法舒地尔作为新型的钙离子拮抗剂,可通过抑制钙离子活动起到拮抗血管收缩作用^[19]。近年来,随着法舒地尔注射液临床应用及药理研究的逐渐深入,其被应用于治疗蛛网膜下腔出血。Satoh S 等^[20]研究发现法舒地尔可提高动脉瘤性蛛网膜下腔出血患者血流速度,改善神经功能。动物试验表明^[21]法舒地尔可缓解小鼠脑组织氧供不足状态,增强其抗氧化损伤的能力,抑制炎症因子的释放,阻止血管平滑肌收缩。本研究显示腰大池引流联合法舒地尔组总有效率较脑脊液置换组高,证实二者的疗效,可能因为二者联合可起到互补作用,从而有效防治蛛网膜下腔出血所致的脑损伤,保护脑功能。

研究显示^[22]动脉瘤性蛛网膜下腔出血中分子生物学可起到至关重要的作用,脑损伤和细胞毒性脑水肿、血脑屏障通透性变化、神经组织的代谢紊乱及变性凋亡有良好相关性,在病情评估及治疗中有重要的参考价值。sICAM-1 为免疫球蛋白超家族成员,正常生理状态下浓度较低,受到炎症等刺激后可在多种细胞中表达,以介导血管内皮细胞及白细胞粘附,参与免疫应答、炎症反应等^[23]。动脉瘤性蛛网膜下腔出血患者因颅脑组织损伤及脑动脉壁的继发炎症诱导 sICAM-1 表达,具有炎性损伤效应。FABP 能够调节细胞内脂肪酸水平,动脉瘤性蛛网膜下腔出血患者 FABP 浓度明显上升,和脑部缺血、缺氧有良好关系^[24]。MCP-1 为趋化因子,能够通过多种途径参与脑部

缺血性损伤,其可激活或者趋化炎性细胞在脑实质中的表达,上调黏附分子浓度,破坏血脑屏障,影响神经修复^[26]。MCP-1 缺失可明显减少巨噬细胞聚集,阻断 MCP-1 生物学活性可明显减轻免疫炎症反应^[25]。本研究结果显示腰大池引流联合法舒地尔治疗的患者治疗后血清 sICAM-1、FABP、MCP-1 水平明显下降,提示二者联合治疗更能有效减轻脑部炎症反应,改善组织缺血、缺氧状态,促进患者恢复,这可能是联合作用效果更好的途径之一,但仍有待进一步的研究证实。

脑积水为动脉瘤性蛛网膜下腔出血的常见并发症,是因脑脊液循环、吸收产生障碍或者过度分泌,增加脑脊液量,从而引起蛛网膜下腔或者脑室系统扩大所致,可出现多种症状,增加患者病死率,临床应加强防治,提高患者预后^[27,28]。既往临床主要为法舒地尔对动脉瘤蛛网膜下腔出血脑痉挛的预防报道,本研究结果显示腰大池引流联合法舒地尔组脑积水率相对较低,说明二者联合更能降低脑积水形成的危险性,考虑与腰大池引流可促进脑脊液生成及回流,从而避免脑脊液回流不畅所致的脑积水,加上法舒地尔能够改善血液循环,减轻局部缺血缺氧损伤,从而降低脑积水可能性^[29,30]。进一步研究分析显示腰大池引流联合法舒地尔组治疗后血压、大脑中动脉血流参数及神经功能改善更明显,证实二者联合应用的可行性。两组均有脑血管痉挛、再出血、肺部感染、胃肠道反应发生,但联合应用组脑痉挛率更低,说明在脑脊液置换基础上加用法舒地尔有利于脑痉挛的控制。

综上所述,腰大池引流联合法舒地尔治疗动脉瘤性蛛网膜下腔出血的疗效明显优于单用腰大池引流治疗,其可显著降低血清 sICAM-1、FABP、MCP-1 水平,降低脑积水发生率,改善患者预后。

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