

doi: 10.13241/j.cnki.pmb.2017.16.033

孕酮对外伤性蛛网膜下腔出血患者早期 MMP-9 水平及微循环的影响 *

李 伟 王 陆 康全利 马更平 崔永胜

(中国医科大学北京顺义医院 神经外科 北京 101300)

摘要 目的:探究孕酮对外伤性蛛网膜下腔出血患者早期 MMP-9 水平及微循环的影响。**方法:**收集我院神经外科收治的外伤性蛛网膜下腔出血患者 70 例,根据随机数字对照表分为对照组(35 例)与试验组(35 例)。两组均给予常规治疗,对照组患者给予静脉注射尼莫地平治疗,试验组在此基础上给予复方甲地孕酮治疗。观察并比较两组患者治疗前后格拉斯哥昏迷指数 GCS 评分、金属基质蛋白酶-9(MMP-9)水平及微循环的变化情况。**结果:**两组患者入院时 GCS 评分、血清 MMP-9 水平无明显差异($P>0.05$),对照组治疗 14 天后 GCS 评分明显升高($P<0.05$),而试验组治疗 7 天、14 天后均明显升高($P<0.05$),且试验组治疗 7 天、14 天后 GCS 评分较对照组评分高($P<0.05$);两组患者治疗 7 天后血清 MMP-9 水平降低($P<0.05$),且试验组血清 MMP-9 水平较对照组降低($P<0.05$);两组患者治疗后微循环均有所改善,伤测大脑中动脉收缩峰流速降低($P<0.05$),试验组改善更为明显,伤测大脑中动脉收缩峰流速降低更为显著($P<0.05$)。**结论:**孕酮对外伤性蛛网膜下腔出血患者的治疗效果明显,可能与其改善微循环,降低血清 MMP-9 水平有关。

关键词:孕酮;外伤性蛛网膜下腔出血;格拉斯哥昏迷指数 GCS 评分;金属基质蛋白酶-9(MMP-9);微循环

中图分类号:R743.35 文献标识码:A 文章编号:1673-6273(2017)16-3129-04

Effects of Progesterone on MMP - 9 Level and Microcirculation in Patients with Early Stage of Traumatic Subarachnoid Hemorrhage*

LI Wei, WANG Lu, KANG Quan-li, MA Geng-ping, CUI Yong-sheng

(Department of Neurosurgery, Beijing Shunyi hospital, China Medical University, Beijing, 101300, China)

ABSTRACT Objective: To investigate the effects of progesterone on the serum MMP - 9 level and microcirculation of patients with early stage of traumatic subarachnoid hemorrhage. **Methods:** A total of 70 cases with traumatic subarachnoid hemorrhage from the neurosurgery department of our hospital were collected and randomly divided into the experimental group and control group with 35 cases in each group. Both groups were given conventional therapy, patients in the control group were treated by stop bleeding, dehydration, hormone and neurotrophic drugs conventional treatment, at the same time with nimodipine 10mg intravenous drip, once a day, continuous administration 14 days. Patients in the experimental group were treated on the basis of the control group with compound megestrol acetate treatment, 25 mg muscle injection, 1 time a day, continuous administration 14 days. After treatment, the GCS score, serum level of MMP9 and change of microcirculation were compared between two groups. **Results:** No obvious difference was found in the GCS score on admission between two groups($P>0.05$). The GCS scores of on the 14th day of both groups were significantly increased after treatment($P<0.05$), the serum MMP-9 level on the 7th day of both groups were significantly decreased after treatment($P<0.05$), the microcirculation were obviously improved after treatment ($P<0.05$). The GCS scores of on the 14th day of experimental group was significantly higher than that of the control group ($P<0.05$), the serum MMP - 9 level was decreased, and the microcirculation improved more significantly after treatment. **Conclusion:** Progesterone had obvious effects on traumatic subarachnoid hemorrhage, which might be related to the improvement of microcirculation and decrease of serum MMP-9 level.

Key words: Progesterone; Traumatic subarachnoid hemorrhage; GCS score; MMP-9; Microcirculation

Chinese Library Classification(CLC): R743.35 **Document code:** A

Article ID: 1673-6273(2017)16-3129-04

外伤性蛛网膜下腔出血 (traumatic subarachnoid hemorrhage, tSAH)通常是由于颅脑外伤导致脑组织挫裂伤,脑组织血管破裂,血液流入到蛛网膜下腔,是颅脑损伤病残和死亡的主要原因之一^[1]。外伤性蛛网膜下腔出血发生后,可引起脑血管痉挛、缺血性神经功能障碍、脑积水等并发症,加重脑组织损伤^[2]。孕酮不仅作为一种性激素,能够治疗生殖系统疾病,同时也

是一种神经甾体激素,对神经系统疾病也能够产生治疗作用^[3,4]。目前,已经有大量动物实验表明孕酮能够减轻炎症反应、减轻水肿、改善微循环,对蛛网膜下腔出血后早期脑损伤有保护作用。基质金属蛋白酶-9(MMP-9)是 MMPs 家族成员的一种,与多种神经系统疾病相关^[5]。有研究表明 MMP-9 在蛛网膜下腔出血早期发挥重要作用^[6]。本研究主要探讨了孕酮对外伤

* 基金项目:北京市自然科学基金项目(2008cdb145)

作者简介:李伟(1979-),男,本科,主治医师,研究方向:颅脑损伤,脑出血,电话:13301212445

(收稿日期:2016-08-24 接受日期:2016-09-21)

性蛛网膜下腔出血患者早期 MMP-9 水平及微循环影响,以期指导临床用药。

1 资料与方法

1.1 临床资料

收集 2014 年 2 月~2016 年 2 月我院神经外科诊治的外伤性蛛网膜下腔出血患者 70 例,纳入标准:① 经 CT、MRI 等影像学检查诊断为蛛网膜下腔出血;② 患者有外伤史;③ 伤后 6 小时内入院;④ GCS 评分 5~10 分;⑤ 经本人或其家属同意参与本试验。排除标准:① 合并严重的复合伤,危及生命;② 入院时颅内血肿形成需要即刻外科手术;③ 患者既往存在严重的心脑血管疾病、恶性肿瘤等;④ 既往有脑梗塞;⑤ 伤后存活时间少于 3 天。所有患者随机分为试验组与对照组,试验组 35 例,男 18 例、女 17 例,平均年龄(38.75 ± 5.13)岁,伤后平均入院时间(3.68 ± 0.57)小时,入院平均 GCS 评分(6.90 ± 1.24)分;对照组 35 例,男 19 例、女 16 例,平均年龄(37.73 ± 5.62)岁,伤后平均入院时间(3.75 ± 0.65)小时,入院平均 GCS 评分(7.04 ± 1.19)分。两组患者年龄、男女比例、伤后入院时间及入院 GCS 评分差异均无统计学意义($P > 0.05$),具有可比性。

1.2 方法

对照组对入院患者给予止血、脱水、激素及神经营养药物等常规治疗,同时静脉注射尼莫地平 10mg(拜耳医药保健有限公司,国药准字 J20100002),每日一次,连续给药 14 天。试验组在上述治疗基础上增加使用复方甲地孕酮(上海通用药业有限公司,国药准字 H31022951)治疗,每次 25mg 肌肉注射,每天 1 次,连续给药 14 天。

1.3 观察指标

1.3.1 GCS 评分 分别在患者入院时及治疗 3 天、7 天、14 天进行 GCS 评分,从睁眼反应、语言反应及肢体运动三个方面对患者昏迷程度进行评分。

1.3.2 微循环功能检测 分别在患者入院时及治疗 7 天、14 天采用彩色经颅多普勒(transcranial doppler, TCD)测定双侧颅内动脉血流情况,记录伤侧大脑中动脉收缩峰流速(Vp)以及通过发射计算机断层摄影(emission computerized tomography, ECT)测定脑损伤部位血供及脑功能情况。彩色经颅多普勒设备购于南京科进实业有限公司。发射计算机断层摄影设备由美国通用公司生产。

1.3.3 血清 MMP-9 水平检测 采集患者入院时及治疗一周后空腹静脉血 5 mL,分布加入枸橼酸抗凝管中,3000 rpm 离心 10 min,提取血浆,采用双抗体夹心酶联免疫吸附检测技术(人 MMP-9 酶联免疫试剂盒,上海西唐生物科技有限公司),检测血清 MMP-9 水平。上述操作均由专业人员按照说明书进行。

1.4 统计学指标

数据处理使用 SPSS13.0 进行统计学分析,计量资料采用均数 $\pm$ 标准差表示,使用 t 检验,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组治疗前后不同时点 GCS 评分的比较

两组患者在入院时及治疗 3 天、7 天、14 天进行 GCS 评分,两组患者入院时 GCS 评分比较差异无统计学意义($P > 0.05$),对照组治疗 14 天后 GCS 评分明显升高($P < 0.05$),而试验组治疗 7 天、14 天后均明显升高($P < 0.05$),且试验组评分较对照组高($P < 0.05$),见表 1。

表 1 两组患者治疗前后不同时间点 GCS 评分的变化比较($\bar{x} \pm s$)

Table 1 Comparison of the GCS score at different time points between two groups before and after treatment($\bar{x} \pm s$)

Groups	On admission	Treatment for 3 days	Treatment for 7 days	Treatment for 14 days
Experimental group (n=35)	6.90 $\pm$ 1.24	6.76 $\pm$ 1.08	9.35 $\pm$ 1.37**	10.82 $\pm$ 2.14**
Control group (n=35)	7.04 $\pm$ 1.19	6.71 $\pm$ 1.42	7.13 $\pm$ 1.20	8.26 $\pm$ 1.87*

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

2.2 两组治疗前后不同时点微循环变化的比较

治疗前,对两组患者行 TCD 及 ECT 检查,TCD 显示两组患者在蛛网膜下腔出血部位的终末端血管紧张度增加,血流加快,伤侧大脑中动脉收缩峰流速均较高,但无统计学意义($P > 0.05$);脑 ECT 显示两组患者在蛛网膜下腔出血部位脑血流减少,出现微循环障碍。治疗 7 天、14 天后,通过 TCD 及 ECT 复

查,在蛛网膜下腔出血部位终末端血管紧张度下降,血流速度改善,微循环障碍改善,伤侧大脑中动脉收缩峰流速降低($P < 0.05$),而试验组相对于对照组,脑血流量、微循环障碍改善明显,伤侧大脑中动脉收缩峰流速降低更为显著($P < 0.05$)说明试验组增加给予孕酮治疗能够改善脑血管微循环障碍,使脑血流得以恢复。

表 2 两组患者治疗前后伤侧大脑中动脉收缩峰流速比较(cm/s, $\bar{x} \pm s$)

Table 2 Comparison of Vp between two groups before and after treatment(cm/s, $\bar{x} \pm s$)

Groups	On admission	Treatment for 3 days	Treatment for 7 days
Experimental group (n=35)	131.24 $\pm$ 20.39	97.18 $\pm$ 16.25**	90.56 $\pm$ 15.36**
Control group (n=35)	133.76 $\pm$ 21.23	121.41 $\pm$ 19.16*	109.70 $\pm$ 18.77*

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

2.3 两组治疗前后不同时血清 MMP-9 水平的比较

两组患者在接受治疗前血清 MMP-9 水平比较差异无统计学意义($P>0.05$)。治疗 7 天后,两组血清 MMP-9 水平均较治疗

前显著降低($P<0.05$),且试验组血清 MMP-9 水平较对照组降低更显著($P<0.05$),见表 2。

表 3 两组患者治疗前血清 MMP-9 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum MMP-9 level between two groups before and after treatment($\bar{x}\pm s$)

Groups	Time	MMP-9(ng/mL)
Experimental group (n=35)	Before treatment	542.17 $\pm$ 36.12
	After treatment	238.49 $\pm$ 22.18**
Control group (n=35)	Before treatment	566.38 $\pm$ 39.44
	After treatment	312.40 $\pm$ 25.75*

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

3 讨论

外伤性蛛网膜下腔出血是由于颅脑外伤所致的脑血管破裂造成血液流入蛛网膜与软脑膜之间的腔隙内,导致偏瘫、昏迷等严重的神经功能损伤^[7]。由于蛛网膜下腔出血可导致脑血管痉挛、脑积水、再出血等并发症,在临床上致死率极高。因此,应在蛛网膜下腔出血早期及时给予干预措施预防脑血管痉挛等并发症,当出现脑血管痉挛时,早期治疗极为重要^[8,9]。研究显示^[10]蛛网膜下腔出血造成脑损伤,使得脑神经细胞、血管内皮细胞、血管平滑肌细胞内钙离子浓度升高,从而导致血管痉挛,脑缺血,引起脑肿胀,造成颅内压升高,而颅内压升高又加重脑缺血,形成恶性循环,使得脑损伤不断加重。目前,钙通道阻滞剂如尼莫地平,能够透过血脑屏障,能够明显改善蛛网膜下腔出血后的微循环障碍,能够抑制钙离子流入血管内皮细胞,能够防止迟发性脑缺血,从而预防并治疗脑血管痉挛^[11,12]。

随着神经保护剂开发与研究的不断进展,研究表明孕酮不仅作为一种性激素能够治疗生殖系统疾病,也是一种神经甾体激素,对神经系统疾病也能够产生治疗作用^[13]。目前,已经有大量动物实验表明孕酮能够减轻炎症反应、减轻水肿、改善微循环,从而对蛛网膜下腔出血后早期脑损伤有保护作用^[14,15]。但是有关孕酮是否能够治疗外伤性蛛网膜下腔出血以及改善微循环尚无报道。本研究以 70 例外伤性蛛网膜下腔出血患者为研究对象,对照组给予注射尼莫地平,试验组在对照组基础上给予肌肉注射复方甲地孕酮,通过对患者治疗前后不同时间点 GCS 评分、TCD、ECT 检查发现对照组治疗 14 天,GCS 评分明显升高,而试验组治疗 7 天、14 天后均有明显升高,且试验组较对照组评分高,治疗 14 天后在蛛网膜下腔出血部位终末端血管紧张度下降,血流速度改善,微循环障碍改善,伤测大脑中动脉收缩峰流速降低,而试验组相对于对照组,脑血流量、微循环障碍改善明显,伤测大脑中动脉收缩峰流速降低更为显著。这些结果说明孕酮具有改善脑血管微循环障碍,使脑血流得以恢复的功效。

MMP-9 为基质金属蛋白酶的一种,神经组织内星形胶质细胞、少突胶质细胞、炎症细胞等均以酶原的形式分泌 MMP-9^[16,17]。有研究表明当蛛网膜下腔出血时,脑组织局部发生严重反应,可引起进一步损伤,MMP-9 作为一种炎性细胞因

子,对于蛛网膜下腔出血的发生发展有关,在蛛网膜下腔出血早期呈现爆发性释放,能够作为反应蛛网膜下腔出血引起的炎症程度的重要指标,同时 MMP-9 水平能够反映预后状况^[18-20]。本研究结果显示试验组患者应用孕酮治疗后早期 MMP-9 水平下降极为明显,说明孕酮能够抑制炎性细胞因子的产生,从而能够缓解蛛网膜下腔出血所致的脑组织损伤,预防并治疗蛛网膜下腔出血引起的血管痉挛等并发症。

综上所述,孕酮对外伤性蛛网膜下腔出血患者的治疗效果明显,可能与其改善微循环,降低血清 MMP-9 水平有关。

参考文献(References)

- [1] Boreczuk P, Penn J, Peak D, et al. Patients with traumatic subarachnoid hemorrhage are at low risk for deterioration or neurosurgical intervention [J]. Journal of Trauma and Acute Care Surgery, 2013, 74 (6): 1504-1509
- [2] Quigley M R, Chew B G, Swartz C E, et al. The clinical significance of isolated traumatic subarachnoid hemorrhage [J]. Journal of Trauma and Acute Care Surgery, 2013, 74(2): 581-584
- [3] Ditty B J, Omar N B, Foreman P M, et al. The nonsurgical nature of patients with subarachnoid or intraparenchymal hemorrhage associated with mild traumatic brain injury [J]. Journal of neurosurgery, 2015, 123(3): 649-653
- [4] Woernle C M, Winkler K M L, Burkhardt J K, et al. Hydrocephalus in 389 patients with aneurysm-associated subarachnoid hemorrhage [J]. Journal of clinical neuroscience, 2013, 20(6): 824-826
- [5] Papanikolaou J, Spathoulas K, Makris D, et al. Hemodynamic challenges in traumatic subarachnoid hemorrhage complicated by cerebral vasospasm [J]. The American journal of emergency medicine, 2016, 34(5): 904-906
- [6] Wassef S N, Abel T J, Grossbach A, et al. Traumatic intracranial hemorrhage in patients taking dabigatran: report of 3 cases and review of the literature [J]. Neurosurgery, 2013, 73(2): E368-E374
- [7] Uhrenholt L, Freeman M D, Webb A L, et al. Fatal subarachnoid hemorrhage associated with internal carotid artery dissection resulting from whiplash trauma [J]. Forensic science, medicine, and pathology, 2015, 11(4): 564-569
- [8] Komori M, Yasaka M, Kokuba K, et al. Intracranial hemorrhage during dabigatran treatment [J]. Circulation Journal, 2014, 78 (6): 1335-1341

- [9] Yuh E L, Mukherjee P, Lingsma H F, et al. Magnetic resonance imaging improves 3 month outcome prediction in mild traumatic brain injury[J]. *Annals of neurology*, 2013, 73(2): 224-235
- [10] Oh J, Lee W, Jang J Y, et al. Delayed Traumatic Subarachnoid Hemorrhage in a Polytraumatized Patient with Disseminated Intravascular Coagulation [J]. *Korean Journal of Critical Care Medicine*, 2015, 30(4): 336-342
- [11] Thelin E P, Johannesson L, Nelson D, et al. S100B is an important outcome predictor in traumatic brain injury [J]. *Journal of neurotrauma*, 2013, 30(7): 519-528
- [12] Lima Oliveira M, Kairalla A C, Fonoff E T, et al. Cerebral microdialysis in traumatic brain injury and subarachnoid hemorrhage: state of the art[J]. *Neurocritical care*, 2014, 21(1): 152-162
- [13] Izzy S, Muehlschlegel S. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage and traumatic brain injury [J]. *Current treatment options in neurology*, 2014, 16(1): 1-16
- [14] Zhao J, Chen Z, Xi G, et al. Deferoxamine attenuates acute hydrocephalus after traumatic brain injury in rats [J]. *Translational stroke research*, 2014, 5(5): 586-594
- [15] Balinger K J, Elmously A, Hoey B A, et al. Selective computed tomographic angiography in traumatic subarachnoid hemorrhage: a pilot study[J]. *Journal of surgical research*, 2015, 199(1): 183-189
- [16] von der Brölie C, Schneegans I, van den Boom L, et al. Impaired coagulation is a risk factor for clinical and radiologic deterioration in patients with traumatic brain injury and isolated traumatic subarachnoid hemorrhage [J]. *Journal of Trauma and Acute Care Surgery*, 2015, 79(2): 295-300
- [17] Kopczak A, Kilimann I, von Rosen F, et al. Screening for hypopituitarism in 509 patients with traumatic brain injury or subarachnoid hemorrhage [J]. *Journal of neurotrauma*, 2014, 31(1): 99-107
- [18] Jabbarli R, Reinhard M, Roelz R, et al. Outcome prediction after non-aneurysmal non-traumatic subarachnoid hemorrhage [J]. *Current neurovascular research*, 2015, 12(3): 269-276
- [19] Marder C P, Narla V, Fink J R, et al. Subarachnoid hemorrhage: beyond aneurysms [J]. *American journal of roentgenology*, 2014, 202(1): 25-37
- [20] Wilson T J, Stetler Jr W R, Al-Holou W N, et al. Management of intracranial hemorrhage in patients with left ventricular assist devices: Clinical article[J]. *Journal of neurosurgery*, 2013, 118(5): 1063-1068

(上接第 3110 页)

- [14] Leite ET, Ugino RT, Santana MA, et al. Incidental irradiation of internal mammary lymph nodes in breast cancer: conventional two-dimensional radiotherapy versus conformal three-dimensional radiotherapy[J]. *Radiol Bras*, 2016, 49(3): 170-175
- [15] Hacıislamoglu E, Colak F, Canyilmaz E, et al. The choice of multi-beam IMRT for whole breast radiotherapy in early-stage right breast cancer[J]. *Springerplus*, 2016, 5(1): 688
- [16] Quadri HS, Hong YK, Al-Refaie WB. Approach to the surgical management of resectable gastric cancer [J]. *Clin Adv Hematol Oncol*, 2016, 14(4): 249-257
- [17] Tesfaye A, Marshall JL, Smaglo BG. Approach to the medical management of surgically resectable gastric cancer [J]. *Clin Adv Hematol Oncol*, 2016, 14(2): 129-135
- [18] Izuishi K, Mori H. Recent Strategies for Treating Stage IV Gastric Cancer: Roles of Palliative Gastrectomy, Chemotherapy, and Radiotherapy[J]. *J Gastrointest Liver Dis*, 2016, 25(1): 87-94
- [19] Nonoshita T, Otsuka S, Inagaki M, et al. Complete Response Obtained with S-1 Plus CDDP Therapy in a Patient with Multiple Liver Metastases from Gastric Cancer[J]. *Hiroshima J Med Sci*, 2015, 64(4): 65-69
- [20] 余一锋,段爱雄. 口服替吉奥联合三维适形放疗治疗局部晚期胃癌疗效观察[J]. *现代肿瘤医学*, 2015, 23(11): 1565-1567
- Yu Yi-feng, Duan Ai-xiong. Study of oral S-1 combined with three dimensional conformal radiotherapy for patients with locally advanced gastric cancer [J]. *Journal of Modern Oncology*, 2015, 23(11): 1565-1567