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依达拉奉联合纳美芬对急性重型颅脑损伤患者血清神经细胞因子和炎性因子的影响*

孙尊鹏 刘荣明△ 葛卫星 严金霞 路玉宇

（南京医科大学附属江宁医院重症医学科 江苏 南京 211100）

摘要 目的:探讨依达拉奉联合纳美芬对急性重型颅脑损伤患者血清神经细胞因子和炎性因子的影响。**方法:**选择2015年1月至2017年12月我院接诊的急性重型颅脑损伤患者80例,按照随机数字表法分为对照组(n=40)和观察组(n=40),对照组患者入院后接受常规综合治疗,观察组在此基础上给予依达拉奉联合纳美芬进行治疗,比较两组患者血清神经细胞因子、炎性因子水平及格拉斯哥昏迷评分(GCS)、急性生理学及慢性健康状况Ⅱ(APACHEⅡ)评分变化情况,观察两组患者颅内压情况、脑水肿情况以及不良反应发生情况。**结果:**观察组患者治疗后1d、治疗后1周血清β-内咖肽、S100β蛋白、神经特异性烯醇化酶(NSE)水平均低于治疗前和对照组(P<0.05)。两组患者治疗后1周血清超敏C反应蛋白(hs-CRP)、肿瘤坏死因子-α(TNF-α)、白细胞介素-8(IL-8)水平均较治疗前降低,且观察组低于对照组(P<0.05)。观察组患者治疗1周后颅内压<15 mmHg所占比例及轻度脑水肿所占比例均高于对照组(P<0.05),而颅内压≥20 mmHg所占比例及重度脑水肿所占比例均著低于对照组(P<0.05)。两组患者治疗后1周GCS评分较治疗前升高,APACHEⅡ评分较治疗前降低(P<0.05);且观察组治疗后1周GCS评分较对照组升高,APACHEⅡ评分较对照组降低(P<0.05)。两组患者不良反应发生率经统计分析差异无统计学意义(P>0.05)。**结论:**依达拉奉联合纳美芬能够明显改善急性重型颅脑损伤患者血清神经细胞因子和炎性因子水平,促进颅内压下降和脑水肿吸收,有利于提升患者预后,且安全性好。

关键词:急性;重型颅脑损伤;依达拉奉;纳美芬;神经细胞因子;炎性因子

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Effect of Edaravone Combined with Nalmefene in Serum Nerve Cell Factors and Inflammatory Factors in Patients with Acute Severe Craniocerebral Injury*

SUN Zun-peng, LIU Rong-ming△, GE Wei-xing, YAN Jin-xia, LU Yu-yu

(Department of Intensive Medicine, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing, Jiangsu, 211100, China)

ABSTRACT Objective: To investigate the effect of edaravone combined with nalmefene in serum nerve cell factors and inflammatory factors in patients with acute severe craniocerebral injury. **Methods:** 80 patients with acute severe brain injury who were received in our hospital from January 2015 to December 2017 were selected, and they were randomly divided into control group(n=40) and observation group (n=40). The patients in the control group were received routine comprehensive treatment after admission, on this basis, the observation group were given edaravone combined with nalmefene treatment. The levels of serum nerve cell factors, inflammatory factors, Glasgow Coma Scale (GCS), acute physiology and chronic health status II (APACHE II) score were compared between the two groups, the intracranial pressure, brain edema and adverse reaction were observed in the two groups. **Results:** The levels of serum β-endorphin, S100β protein and neuron specific enolase (NSE) in the observation group at 1d and 1 week after treatment were lower than those before treatment and in the control group (P<0.05). The levels of serum high sensitivity C reactive protein (hs-CRP), tumor necrosis factor-α(TNF-α), interleukin-8(IL-8) of patients in two groups at 1 week after treatment were lower than before treatment, and the observation group was lower than the control group (P<0.05). The proportion of intracranial pressure <15 mmHg and the proportion of mild cerebral edema at 1 week after treatment in the observation group were higher than that of the control group (P<0.05), proportion of intracranial pressure ≥ 20 mmHg and the proportion of severe brain edema proportion was lower than that of the control group (P<0.05). The score of GCS in the two groups was higher than that before treatment at 1 week after treatment, and the score of APACHE II was lower than that before treatment(P<0.05). The score of GCS in the observation group was higher than that of the control group at 1 week after treatment, and the score of APACHE II was lower than that of the control group(P<0.05). There was no statistically significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Edaravone combined with

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作者简介:孙尊鹏(1979-),男,本科,主治医师,从事重症医学方面的研究,E-mail:yubgtg@163.com

△ 通讯作者:刘荣明(1986-),男,本科,主治医师,从事重症医学方面的研究,E-mail:outerg@163.com

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nalmefene can significantly improve nerve cell factors and inflammatory factors levels of patients with acute severe craniocerebral injury, and it promotes the reduction of intracranial pressure and the absorption of brain edema, which is beneficial to the prognosis of the patients and has good safety.

Key words: Acute; Severe craniocerebral injury; Edaravone; Nalmefene; Nerve cell factor; Inflammatory factor

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前言

急性重型颅脑损伤是临床常见的急危重症，随着近几年国内交通事故、工伤事故以及高空坠物事件发生频率的增加，急性重型颅脑损伤发病率也呈逐年升高的趋势，已经引起了临床医师的普遍关注[1,2]。由于急性重型颅脑损伤除创伤本身的损伤外常因脑缺血、缺氧以及脑创伤等严重应激刺激而继发脑组织损伤，因此致残率和致死率均较高[3,4]。有关专家指出，急性重型颅脑损伤后短时间内的内源性阿片肽与氧自由基的过度表达极易诱发神经元细胞的损伤、变性及凋亡，同时也会破坏血脑屏障，造成急性脑水肿[5]。因此，除常规有效救治措施外，对脑和神经组织实施保护性治疗也是提升患者预后的关键[6,7]。依达拉奉是氧自由基清除剂，而纳美芬属内源性阿片肽受体阻断剂，二者配合使用能够针对性抑制内源性阿片肽与氧自由基的过度表达，从而对脑和神经组织起到保护效果[8-10]。本研究通过研究依达拉奉联合纳美芬对急性重型颅脑损伤患者血清神经细胞因子和炎性因子的影响，以期为该病的临床治疗提供参考依据，现报道如下。

1 资料与方法

1.1 一般资料

将 2015 年 1 月至 2017 年 12 月我院接诊的急性重型颅脑损伤患者 80 例纳入本研究。纳入标准：(1)经常规颅脑影像学检查确诊者；(2)发病后 2-12 h 内入院治疗者；(3)均签署知情同意书。排除标准：(1)开放性颅脑损伤者；(2)合并多发损伤、复合伤或脑脊液漏者；(3) 合并其他重要脏器功能障碍者；(4)有精神疾病或交流障碍者。按照随机数字表法分为观察组(n=40)和对照组(n=40)。观察组男性 26 例，女性 14 例；年龄为 22-68 岁，平均(45.22± 6.85)岁；致伤原因：交通事故 25 例、高空坠物砸伤 7 例、高处坠落 5 例、暴力伤 3 例。对照组男性 27 例，女性 13 例；年龄为 21-65 岁，平均(46.17± 6.77)岁；致伤原因：交通事故 26 例、高空坠物砸伤 6 例、高处坠落 6 例、暴力伤 2 例。比较两组患者的基线资料差异无统计学意义(P>0.05)，均衡可比。本研究经我院伦理委员会批准同意。

1.2 方法

对照组患者入院后即接受常规综合治疗，包括脱水、降颅压、纠正水电解质失衡、吸氧、抗感染、脑神经营养等对症治疗，必要时实施手术。观察组患者在此基础上给予依达拉奉(河北医科大学生物医学工程中心，国药准字：H20090353，规格：20 mL:30 mg)联合纳美芬(西安利君制药有限责任公司，国药准字：H20120020，规格：1 mL: 0.1 mg)治疗：依达拉奉 60 mg/d，静脉滴注；纳美芬首剂量 0.4 mg/(kg·d)，连用 3 d 后改为 0.2 mg/(kg·d)，至第 7 d 后改为 0.1 mg/(kg·d)，静脉滴注。两组均治疗 2周。

1.3 观察指标

分别于治疗前、治疗后 1 d、治疗后 1 周抽取患者清晨空腹外周静脉血 10 mL，使用 2500 r/min 离心机离心 10 min 后，采用酶联免疫吸附法检测 β- 内咖肽、神经特异性烯醇化酶(neuron specific enolase，NSE)、S100β 蛋白水平，采用免疫比浊法检测血清肿瘤坏死因子 -α（tumour necrosis factor-α，TNF-α)、超敏 C 反应蛋白（high-sensitivity C-reactive protein，hs-CRP)、白细胞介素 -8(interleukin-8，IL-8)水平，以上指标试剂盒均购自上海信裕生物科技有限公司。比较治疗前、治疗后 1 周两组患者格拉斯哥昏迷评分(Glasgow coma score，GCS)、急性生理学及慢性健康状况Ⅱ(Acute physiology and chronic health evaluationⅡ，APACHEⅡ)评分，其中 GCS 评分总分共 15 分，包含语言反应、睁眼反应和肢体运动，评分越低表示昏迷程度越深[11]。APACHEⅡ评分包含急性生理评分、年龄评分和慢性健康评分三方面，最高分 71 分，≥ 15 分为重症，评分越高表示病情越严重[12]。采用颅内压无创综合检测分析仪 JYH_ICP-1B-S(上海斯欧医疗器械有限公司)测定两组患者颅内压情况，并对脑水肿情况以及不良反应发生情况进行分析，其中脑水肿严重程度分级标准：轻度：CT 影像显示水肿带直径低于 2 cm；中度：水肿带直径超过 2 cm，但低于 1/2 半球面积；重度：水肿带直径超过 1/2 半球面积。

1.4 统计学方法

使用 SPSS 19.0 进行统计学处理，性别构成、不良反应率以及颅内压、脑水肿占比等计数资料以百分率表示，组间比较用 χ^2 检验，神经细胞因子、炎性因子水平以及 GCS、APACHEⅡ评分等计量资料以均数± 标准差($\bar{x}\pm s$)表示，组间比较用 t 检验，检验标准设置为α=0.05。

2 结果

2.1 两组患者血清神经细胞因子水平对比

两组患者治疗前血清神经细胞因子水平经统计分析差异无统计学意义(P>0.05)。观察组患者治疗后 1d、治疗后 1 周血清 β- 内咖肽、S100β 蛋白、NSE 水平均低于治疗前和对照组(P<0.05)，对照组治疗后 1 周血清 β- 内咖肽、S100β 蛋白、NSE 水平低于治疗前(P<0.05)，见表 1。

2.2 两组患者血清炎性因子水平对比

两组患者治疗前血清炎性因子水平经统计分析差异无统计学意义(P>0.05)。两组患者治疗后 1 周血清 hs-CRP、TNF-α、IL-8 水平均较治疗前降低，且观察组低于对照组(P<0.05)，见表 2。

2.3 两组患者治疗后 1 周颅内压及脑水肿情况对比

观察组患者治疗 1 周后颅内压 <15 mmHg 所占比例及轻度脑水肿所占比例均高于对照组（P<0.05），而颅内压≥

20 mmHg 所占比例及重度脑水肿所占比例均著低于对照组（P<0.05）。两组患者治疗 1 周后颅内压 15-20 mmHg 所占比例及中度脑水肿所占比例比较差异无统计学意义（P>0.05）。见表 3。

表 1 两组患者血清神经细胞因子水平对比（$\bar{x}\pm s$）

Table 1 Comparison of serum neurokine levels between the two groups($\bar{x}\pm s$)

Groups	Time	β-endorphin(ng/L)	S100β protein(μg/L)	NSE(μg/L)
Observation group(n=40)	Before treatment	231.47± 15.65	1.18± 0.22	35.65± 4.73
	1 d after treatment	198.95± 13.22△ *	0.85± 0.23△ *	25.11± 3.62△ *
	1 week after treatment	171.02± 11.47△ *	0.66± 0.17△ *	17.94± 2.91△ *
Control group(n=40)	Before treatment	230.95± 15.88	1.17± 0.25	35.63± 4.49
	1 d after treatment	229.25± 14.39	1.10± 0.22	34.02± 4.17
	1 week after treatment	218.06± 14.68△	0.89± 0.20△	27.18± 3.66△

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

表 2 两组患者血清炎性因子水平对比（$\bar{x}\pm s$）

Table 2 Comparison of serum inflammatory factors levels between the two groups($\bar{x}\pm s$)

Groups	Time	hs-CRP(mg/L)	TNF-α(μg/L)	IL-8(μg/L)
Observation group(n=40)	Before treatment	3.41± 0.33	3.93± 0.47	2.10± 0.40
	1 week after treatment	1.61± 0.31△ *	1.69± 0.37△ *	0.68± 0.13△ *
Control group(n=40)	Before treatment	3.43± 0.35	3.90± 0.50	2.11± 0.42
	1 week after treatment	2.31± 0.39△	2.34± 0.66△	1.31± 0.30△

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

表 3 两组患者治疗 1 周后颅内压及脑水肿情况对比[n(%)]

Table 3 Comparison of intracranial pressure and brain edema between the two groups 1 week after treatment[n(%)]

Groups	Intracranial pressure(mmHg)			Brain edema		
	<15	15-20	≥ 20	Light	Moderate	Severe
Observation group(n=40)	12(30.00)	17(42.50)	11(27.50)	19(47.50)	17(42.50)	4(10.00)
Control group(n=40)	3(7.50)	16(40.00)	21(52.50)	8(20.00)	20(50.00)	12(30.00)
x^2	6.646	0.052	5.208	6.765	0.453	5.000
P	0.010	0.820	0.022	0.009	0.501	0.025

2.4 两组患者 GCS 评分及 APACHEⅡ评分对比

两组患者治疗前 GCS 评分、APACHEⅡ评分经统计分析差异无统计学意义（P>0.05）。两组患者治疗后 1 周 GCS 评分较治疗前升高，APACHEⅡ评分较治疗前下降（P<0.05）；且观察组治疗后 1 周 GCS 评分较对照组升高，APACHEⅡ评分较对照组降低（P<0.05），见表 4。

表 4 两组患者 GCS 评分及 APACHEⅡ评分对比（分，$\bar{x}\pm s$）

Table 4 Comparison of GCS score and APACHE II score between the two groups(scores, $\bar{x}\pm s$)

Groups	GCS		APACHEⅡ	
	Before treatment	1 week after treatment	Before treatment	1 week after treatment
Observation group(n=40)	5.75± 1.07	9.33± 1.58△	18.58± 3.17	12.89± 1.46△
Control group(n=40)	5.39± 1.02	7.20± 1.41△	17.23± 3.25	15.33± 2.01△
t	1.540	6.361	1.881	6.212
P	0.128	0.000	0.064	0.000

Note: Compared with before treatment, △ P<0.05.

2.5 两组患者不良反应发生情况对比

两组患者恶心 / 呕吐、腹泻、便秘等发生率经统计分析差异无统计学意义（P>0.05），见表 5。

3 讨论

急性重型颅脑损伤发病机制复杂，目前尚未完全明确，采

表 5 两组患者不良反应发生情况对比[n(%)]

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

Groups	Nausea/vomiting	Diarrhea	Constipation	Total
Observation group(n=40)	7(17.50)	1(2.50)	1(2.50)	9(22.50)
Control group(n=40)	6(15.00)	1(2.50)	0(0.00)	7(17.50)
x^2				0.313
P				0.576

取及时有效的干预措施是降低致残率和死亡率的关键[13,14]。临床研究表明，急性重型颅脑损伤除原发创伤所致的脑血管、神经组织损伤外，颅内血肿占位、手术创伤以及应激反应均易诱发脑水肿、颅内压升高、脑缺血、神经细胞损伤等继发性脑损伤，大大增加了治疗难度[15-17]。相关国内外报道指出，急性重型颅脑损伤后内源性阿片肽与氧自由基的过度表达是造成急性重型颅脑损伤患者脑损伤的主要危险因素，内源性阿片肽与氧自由基参与了脑水肿、颅内压升高、脑缺血、神经细胞损伤等继发性脑损害过程，采取针对性药物干预治疗是提升患者预后的关键[18,19]。目前，急性重型颅脑损伤的脑保护治疗已经成为了临床研究的热点。

本研究中所用的依达拉奉与纳美芬均为一线脑保护药物，其中依达拉奉为自由基清除剂，能够对急性重型颅脑损伤后脑组织缺血缺氧时发生的细胞脂质代谢和氧自由基大量生成过程产生抑制作用，从而减轻血管内皮损伤，达到保护神经和胶质细胞的作用[20,21]。另外，依达拉奉还可抑制氧自由基对线粒体的破坏，有效减少 Ca^{2+} 内流，从而可维持患者缺血状态下细胞内 Ca^{2+} 与 Mg^{2+} 的平衡，并且对促进氧化磷酸化与能量供给恢复以及进一步减轻神经、胶质细胞损伤和凋亡有积极意义[22]。而纳美芬则为新型阿片受体拮抗剂，能竞争性拮抗各类阿片受体，尤其对μ 受体有很强的亲和力[23]。该药物起效快、半衰期长，短时间内即可达到较高的血药浓度，能够通过特异性阻断 β- 内咖肽与阿片受体的结合，从而阻断内源性阿片肽诱发的多种继发性脑损伤[24]。现代药理学研究还显示，纳美芬具有纠正重型颅脑损伤患者水电解质紊乱、促进脑细胞代谢、改善脑供血和脑水肿等作用，保护脑功能效果明显[25]。

本研究中将依达拉奉与纳美芬联用，由于二者作用机制并不相同，因此有一定协同互补效果，观察组患者治疗 1 周后颅内压 <15 mmHg 所占比例及轻度脑水肿所占比例均高于对照组，这也证实了该方案在降低颅内压和减轻脑水肿方面的显著作用。本研究结果还显示，观察组的治疗方法对降低血清神经细胞因子水平效果更显著，分析原因主要为依达拉奉与纳美芬均有减轻神经、胶质细胞损伤和凋亡的效果，有效抑制了急性重型颅脑损伤患者 β- 内咖肽水平异常升高以及 S100β 蛋白、NSE 从神经胶质细胞与神经元中逸出的情况。本研究中两组患者经治疗后血清炎性因子水平均得到改善，并且观察组的改善效果更好，分析其原因主要与纳美芬能够调节重型颅脑损伤患者异常的炎性反应，减轻应激状态下机体的损伤有关。另外，观察组治疗后 1 周 GCS 评分较对照组升高，APACHE Ⅱ 评分较对照组降低，也从侧面证实了依达拉奉与纳美芬联用能够保护脑功能，快速逆转意识障碍，解除呼吸抑制作用，降低颅内压，缓解脑水肿，短时间内减轻患者病情。最后，在不良反应方面药理学研究表明依达拉奉与纳美芬均无明显不良反应，本研究中两组不良反应发生率对比差异无统计学意义（P>0.05），也证实了在常规综合治疗基础上加用依达拉奉与纳美芬并不会明显增加不良反应，安全性较好。

综上所述，依达拉奉联合纳美芬治疗急性重型颅脑损伤患者安全有效，可降低患者炎症反应，改善颅内压及脑水肿情况和神经细胞因子水平，缓解病情。

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