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依达拉奉联合尼莫地平对颅脑损伤患者氧化应激、炎症因子的影响

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[摘要] **目的**:观察依达拉奉联合尼莫地平对颅脑损伤患者氧化应激、炎症因子的影响。**方法**:将126例颅脑损伤病例随机分为观察组(66例)和对照组(60例)。对照组在常规治疗的基础上给予尼莫地平,观察组在对照组的基础上给予依达拉奉。治疗14 d,观察两组氧化应激指标(SOD、MPO、MDA)、炎症因子(CRP、TNF-α、IL-8)的变化。**结果**:(1)两组SOD、MPO、MDA水平比较差异有统计学意义($P<0.05$),两组MPO、MDA、LPO随着时间的延长表现出先升高后降低的趋势($P<0.05$),观察组SOD升高的幅度大于对照组而MPO、MDA升高的幅度小于对照组($P<0.05$);(2)两组TNF-α、CRP、IL-8水平比较差异有统计学意义($P<0.05$),两组TNF-α、CRP、IL-8随着时间的延长表现出先升高后降低的趋势($P<0.05$),观察组升高的幅度小于对照组($P<0.05$)。**结论**:依达拉奉联合尼莫地平应用于颅脑损伤时抑制氧化应激、炎症反应作用显著,优于单用尼莫地平。

[关键词] 颅脑损伤;依达拉奉;尼莫地平;氧化应激;炎症因子
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Effect of edaravone combined with nimodipine on oxidative stress, inflammatory factors in patients with craniocerebral injury

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] **Objective**: To observe the effect of edaravone combined with nimodipine on oxidative stress, inflammatory factors in patients with craniocerebral injury. **Methods**: A total of 126 patients with craniocerebral injury were randomly divided into the observation group (66 cases) and the control group (60 cases). The control group was given nimodipine based on conventional therapy, and the observation was given edaravone based on the control group. For 14 days, the changes of oxidative stress indicators (SOD, MPO, MDA) and inflammatory factors (CRP, TNF-α, IL-8) between the two groups were observed. **Results**: There was significantly difference in SOD, MPO, MDA in these two groups ($F_{group}=5.483, 6.275, 6.561$, $P<0.05$), they were all showed a rising then reducing trend over time ($F_{time}=13.062, 8.172, 7.842$, $P<0.05$), the rising amplitude of

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SOD in observation group was less than the control group and MPO, MDA was more than the control group ($F_{interaction}$=5.305, 4.631, 5.327, P<0.05). There was significantly difference of TNF-α, CRP, IL-8 in these two groups (F_{group}=9.308, 10.375, 11.350, P<0.05), they were all showed a rising then reducing trend over time (F_{time}=9.308, 10.375, 11.350, P<0.05), the rising amplitude in observation group was less than the control group ($F_{interaction}$=5.071, 4.736, 6.347, P<0.05). Conclusions Edaravone combined with nimodipine can inhibits oxidative stress and inflammatory reaction significantly in craniocerebral injury, and better than nimodipine alone.

[KEY WORDS] Craniocerebral injury; Edaravone; Nimodipine; Oxidative stress; Inflammatory factors

颅脑损伤是是临床急危重症，及时、有效的治疗是改善预后的关键，保护神经细胞以及减轻其继发性受损至关重要[1]。尼莫地平是公认的脑保护剂，应用历史较长，临床疗效确切；依达拉奉是新型自由基清除剂，在脑梗死[2,3]的应用中显示其脑保护作用卓著，目前也逐渐应用于颅脑损伤的救治中。近年来依达拉奉与尼莫地平联合应用于颅脑损伤日趋增多，但相关报道尚为少见，本研究通过观察联合应用对颅脑损伤患者氧化应激、炎症因子的影响，明确该方案的有效性。

1 资料与方法

1.1 一般资料与方法

全部病例来源于2014年2月～2016年2月我科收治的颅脑损伤患者，选择伤后12 h内入院的病例纳入研究。排除及剔除标准：(1)合并心肝、肺肾严重疾病，甲状腺功能亢进及肿瘤患者；(2)贯通性颅脑损伤，或双侧瞳孔已等大固定；(3)既往存在严重颅脑损伤，或癫痫病人；(4)生命体征不稳定，氧分压<60 mmHg和(或)收缩压<90 mmHg；(5)存在药物滥用或酗酒者；(6)临床资料不全，治疗期间死亡或转院病例；(7)法定代理人未签署知情同意书者。共126例纳入研究，抽签随机分为观察组和对照组。观察组66例，其中男性41例，女性25例；年龄35～73(47.52±16.64)岁；格拉斯昏迷评分(GLS)4～12(8.21±3.67)分；颅脑损伤类型：脑挫裂伤31例，硬膜外血肿18例，硬膜下血肿12例，颅内血肿5例；保守治疗45例，手术治疗21例。对照组60例，其中男性39例，女性21例；年龄36～72(48.78±17.35)岁；GLS 4～12(8.45±3.57)分；颅脑损伤类型：脑挫伤28例，硬膜外血肿17例；硬膜下血肿11例，颅内血肿4例；保守治疗41例，手术治疗19例。两组一般资料比较差异无统计学意义(P>0.05)。

1.2 治疗方法

所有病例纳入研究后均给予常规治疗，包括：吸氧、控制颅内压、营养脑神经、改善微循环、扩血管以及抗感染。镇静镇痛等治疗，维持水、电解质及酸碱平衡。有手术需要者依据颅脑损伤类型给予血肿清除术、开颅血肿清除术或骨瓣减压术。对照组组在常规处理的基础上给予尼莫地平(生产商：西安杨森制药有限公司 国药准字：J20090130)，用法为：前5天静脉泵入10 mg/d，之后改为口服60 mg/次，日3次，共用14 d；观察组在对照组的基础上给予依达拉奉(生产商：福建天泉药业股份有限公司 国药准字 H20110090)，用法为：30 mg/次，日2次，连用14 d。

1.3 观察指标

主要为：(1)氧化应激指标 超氧化物歧化酶(SOD)、丙二醛(MDA)及髓过氧化物酶(MPO)。均采用比色法原理测定，试剂盒产自南京建成生物工程研究所；(2)炎性因子 C反应蛋白(CRP)、肿瘤坏死因子(TNF-α)、白介素-8(IL-8)。TNF-α、IL-6采用酶联免疫吸附法(ELISA)检测，试剂盒产自北京晶美生物技术有限公司；CRP采用免疫比浊法检测，试剂盒产自 RANDOX 公司。留取静脉血，于治疗前及治疗后第3 d、7 d、14 d各检测1次。

1.4 统计学处理

采用SPSS17.0软件处理。计量资料采用 表示，采用重复测量方差分析。P<0.05认为差异有统计学意义。

2 结果

2.1 两组氧化应激指标比较

两组SOD、MPO、MDA水平比较差异有统计学意义(P<0.05)，两组MPO、MDA、LPO随着时间的延长表现出先升高后降低的趋势(P<0.05)，观察组SOD升高的幅度大于对照组而MPO、MDA升高的幅度小于对照组(P<0.05)。见表1。

表1 两组治疗前后氧化应激指标水平比较($\bar{x}\pm s$)

组别	时间	SOD (U/mL)	MDA (μmol/mL)	MPO (mg/L)
观察组(66例)	治疗前	67.54±17.43	6.77±1.16	1.56±0.43
	治疗3 d	124.35±21.45	9.79±2.84	3.41±0.87
	治疗7 d	112.13±23.30	8.46±2.36	2.51±0.54
	治疗14 d	104.17±18.23	7.35±1.83	1.92±0.38
对照组(60例)	治疗前	65.84±21.33	6.69±1.35	1.52±0.39
	治疗3 d	102.46±24.16	12.14±3.02	4.61±1.01
	治疗7 d	104.13±20.72	10.19±2.26	3.25±0.74
	治疗14 d	100.54±17.34	9.21±2.39	2.37±0.52

2.2 两组治疗前后炎症因子比较

两组TNF-α、CRP、IL-8水平比较差异有统计学意义(P<0.05)，两组TNF-α、CRP、IL-8随着时间的延长表现出先升高后降低的趋势(P<0.05)，观察组升高的幅度小于对照组(P<0.05)。见表2。

表 2 两组治疗前后炎症因子水平比较($\bar{x}\pm s$)

组别	时间	TNF-α (ng/L)	CRP (mg/L)	IL-8 (pg/mL)
观察组(66 例)	治疗前	24.87±8.32	35.36±17.43	225.34±47.65
	治疗 3 d	35.13±11.49	47.24±14.71	265.73±54.87
	治疗 7 d	13.34±5.01	29.54±15.10	202.82±42.90
	治疗 14 d	29.96±13.95	14.46±7.47	147.40±51.69
对照组(60 例)	治疗前	25.22±8.51	49.25±18.46	221.79±51.04
	治疗 3 d	44.46±13.36	44.52±16.14	306.37±61.23
	治疗 7 d	23.41±9.34	33.57±13.53	247.09±52.44
	治疗 14 d	18.84±7.02	20.38±10.42	186.42±34.24

3 讨论

颅脑外伤发生后除存在原发性脑损伤外，亦继发性脑损伤，当后者控制不佳时对机体的不良影响甚至可超过前者[4]，成为预后不良的主要危险因素。继发性脑损伤发生的病理生理过程复杂，氧化应激、炎症反应是其中重要环节[5]，其他因素诸如脑缺血缺氧、脑水肿、脑代谢障碍、缺血再灌注损伤等均与它们有密切关系。氧化应激与炎症反应均可直接损伤神经细胞[6]，亦可造成脑血管痉挛、血液高凝、微循环障碍等使脑缺血缺氧加重而继续损害神经细胞，而如它们激活血小板造成血栓形成诱发脑梗死[7,8]，那后果更为严重。此外，剧烈的氧化应激、炎症反应可诱发机体重要脏器血供不足，引起肺、肾损害[9]；或引起免疫功能抑制而加重颅内及全身感染的风险[10,11]。可见颅脑损伤时控制氧化应激、炎症反应的重要性，炎症反应可使氧化应激加重[12]，而氧化应激反应刺激炎症介质释放可引起炎症级联反应[13]。本研究中观察的氧化应激指标为 SOD、MPO、MDA，SOD 为抗氧化物质，在颅脑损伤发生后因对抗大量生成自由基而过度消耗，活性低于正常人群[14]；MPO 为氧化物质，可刺激自由基产生，MDA 为氧化代谢产物，这两种在颅脑损伤发生后血清含量快速上升[15]。观察的炎症因子为 TNF-α、CRP、IL-8，均为常用检测指标，且均属于促炎症细胞因子[16]，这些指标在颅脑损伤发生后也快速上升。

尼莫地平为钙离子拮抗剂，可抑制钙离子内流入而减少细胞凋亡，同时其有改善红细胞变形能力、改善血流变以及降低血-脑屏障通透性等作用而增加脑组织供血、供氧，通过这些作用可起到保护神经细胞的作用[17]。同时其抑制血小板聚集、改善缺血缺氧状态可有助于抑制氧化应激、炎症反应进一步减少神经细胞损伤，在颅脑损伤治疗中的长期应用充分证实了其有效性[18,19]。依达拉奉为强效自由基清除剂及抗氧化剂，能大量清除自由基及抑制脂质氧化，且有抑制脑水肿、减轻血管内皮损伤及减少缺血半暗带面积的作用，在脑梗死中的大量应用证实了该药的有效性[2,20]。脑梗死与颅脑损伤病理生理基础极其相似[21]，这也是近几年来其在后者中应用增加的理论基础，而逐步可见的报道也对此持证面评价[22]。分析可见，尼莫地平与依达拉奉脑保护作用机制不同，二者联用应有协同作用。

本研究结果显示，观察组治疗后 SOD 明显高于而 MPO、MDA 水平明显低于对照组，提示依达拉奉与尼莫地平联用可有效增加机体抗氧化能力，且有效抑制氧化能力的表达，优于单用尼莫地平；观察组治疗后 TNF-α、CRP、IL-8 均明显低于对照组，提示二者联用抑制机体炎症反应的作用优于单用尼莫地平。观察组氧化应激、炎症反应控制优于对照组，则意味着该组患者可从依达拉奉与尼莫地平联用中获益，可以预期这一方案将有更大的用武之地。

参考文献

1 Thomas AG, Hegde SV, Dineen R A, et al. Patterns of accidental craniocerebral injury occurring in early childhood[J]. Archives of disease in childhood, 2013, 98(10): 787-792.

2 刘振宇,王丽华,周俊英,等.依达拉奉联合尤瑞克林治疗对急性脑梗死患者血液流变学及血管内皮细胞功能的影响[J].海南医学院学报,2014,20(3):337-339,343.

3 李凯，周杰，车万民，等. 依达拉奉对中、重型颅脑损伤患者脑水肿及预后的影响[J].实用临床医药杂志,2014(16):128-130.

4 Zack F, Rodewald AK, Blaas V, et al. Histologic spectrum of the cardiac conducting tissue in non-natural deaths under 30 years of age: an analysis of 43 cases with special implications for sudden cardiac death[J]. International journal of legal medicine, 2016, 130(1): 173-178.

5 Ohta M, Higashi Y, Yawata T, et al. Attenuation of axonal injury and oxidative stress by edaravone protects against cognitive impairments after traumatic brain injury[J]. Brain research, 2013, 1490: 184-192.

6 Sun YY, Li Y, Wali B, et al. Prophylactic Edaravone Prevents Transient Hypoxic-Ischemic Brain Injury Implications for Perioperative Neuroprotection[J]. Stroke, 2015, 46(7): 1947-1955.

7 Uchiyama M, Tojo K, Yazawa T, et al. Edaravone prevents lung injury induced by hepatic ischemia - reperfusion[J]. journal of surgical research, 2015, 194(2): 551-557.

8 Schoeler M, Loetscher PD, Rossaint R, et al. Dexmedetomidine is neuroprotective in an in vitro model for traumatic brain injury[J]. BMC neurology, 2012, 12(1): 1.

9 Ren X, Ma H, Zuo Z. Dexmedetomidine Postconditioning Reduces Brain Injury after Brain Hypoxia-Ischemia in Neonatal Rats[J]. Journal of Neuroimmune Pharmacology, 2016, 11(2): 238-247.

10 Kimura K, Aoki J, Sakamoto Y, et al. Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients-A preliminary study[J]. Journal of the neurological sciences, 2012, 313(1): 132-136.

11 Cai Y, Xu H, Yan J, et al. Molecular targets and mechanism of action of dexmedetomidine in treatment of ischemia/reperfusion injury[J]. Molecular medicine reports, 2014, 9(5): 1542-1550.

(下转第 2534 页)

usal Women: The Global Longitudinal Study of Osteoporosis in Women [J].J Bone Miner Res, 2016, 31(7):1466-1472.
9 Saarelainen J, Hassi S, Honkanen R, et al. Bone loss and wrist fractures after withdrawal of hormone therapy: The 15-year follow-up of the OSTPRE cohort [J].Maturitas, 2016, 85:49-55.
10 Daswani B, Desai M, Mitra S, et al. Influence of bone mineral density measurement on fracture risk assessment tool scores in postmenopausal Indian women [J]. Post Reprod Health, 2016, 22(1):20-24.
11 Boutroy S, Khosla S, Sornay-Rendu E, et al. Microarchitecture and Peripheral BMD are Impaired in Postmenopausal White Women With Fracture Independently of Total Hip T-Score: An International Multicenter Study[J].J Bone Miner Res, 2016, 31(6):1158-1166.
12 Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis [J].N Engl J Med, 2016, 374(3):254-262.
13 Chao AS, Chen FP, Lin YC, et al. Application of the World Health Organization Fracture Risk Assessment Tool to predict need for dual-energy X-ray absorptiometry scanning in postmenopausal women [J]. Taiwan J ObstetGynecol, 2015, 54(6): 722-725.
14 颜建湘,蔡思清,吕国荣,等. 双能 X 线骨密度仪评估绝经后妇女椎体脆性骨折及相关危险因素的分析[J]. 重庆医科大学学报,2015,40(2):216-220.
15 Pavel OR, Popescu M, Novac L, et al. Postmenopausal osteoporosis - clinical, biological and histopathological aspects [J]. Rom J MorpholEmbryol, 2016, 57(1):121-130.
16 Krege JH, Lane NE, Harris JM, et al. PINP as a biological response marker during teriparatide treatment for osteoporosis [J].OsteoporosInt, 2014, 25(9): 2159-2171.
17 Naeem ST, Hussain R, Raheem A, et al. Bone Turnover Markers for Osteoporosis Status Assessment at Baseline in Postmenopausal Pakistani Females [J].J Coll Physicians Surg Pak, 2016, 26(5):408-412.
18 Chavassieux P, Portero-Muzy N, Roux JP, et al. Are Biochemical Markers of Bone Turnover Representative of Bone Histomorphometry in 370 Postmenopausal Women? [J]. J ClinEndocrinolMetab, 2015, 100(12):4662-4668.
19 Wei QS, Huang L, Tan X, et al. Serum osteopontin levels in relation to bone mineral density and bone turnover markers in postmenopausal women[J].Scand J Clin Lab Invest, 2016, 76(1):33-39.
20 Arantes HP, Gimeno SG, Chiang AY, et al. Incidence of vertebral fractures in calcium and vitamin D-supplemented postmenopausal Brazilian women with osteopenia or osteoporosis: data from Arzoxifene Generations Trial [J]. Arch Endocrinol-Metab, 2016, 60(1):54-59.

(上接第 2529 页)

12 Vermaelen J, Greiffenstein P. Sleep in traumatic brain injury [J]. Critical care clinics, 2015, 31(3): 551-561.
13 Gupta O P, Roy K, Ghosh S, et al. An unusual penetrating transorbital craniocerebral injury[J]. The Indian journal of neurotrauma, 2014, 11(1): 53-56.
14 Abdul-Muneer P M, Chandra N, Haorah J. Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury[J]. Molecular neurobiology, 2015, 51(3): 966-979.
15 Rodriguez-Rodriguez A, Jose Egea-Guerrero J, Murillo-Cabezas F, et al. Oxidative stress in traumatic brain injury[J]. Current medicinal chemistry, 2014, 21(10): 1201-1211.
16 Wahlström MR, Olivecrona M, Ahlm C, et al. Effects of prostacyclin on the early inflammatory response in patients with traumatic brain injury-a randomised clinical study[J]. SpringerPlus, 2014, 3(1): 1.
17 Woo PYM, See KWM, Chow J K H, et al. Hypertensive-Nimodipine Therapy for Middle Cerebral Artery Vasospasm after Resection of Glioblastoma Multiforme: A Case Report and Literature Review [J]. Open Journal of Modern Neurosurgery, 2015, 5(03): 76.
18 Koskimäki J, Matsui N, Umemori J, et al. Nimodipine activates TrkB neurotrophin receptors and induces neuroplastic and neuroprotective signaling events in the mouse hippocampus and prefrontal cortex [J]. Cellular and molecular neurobiology, 2015, 35(2): 189-196.
19 Li R. The optimal time window for the use and dosage of nimodipine for acute massive cerebral infarction: study protocol for a randomized controlled trial[J]. Asia Pacific Clinical and Translational Nervous System Diseases, 2016, 1(1): 1.
20 Yuan Y, Zha H, Rangarajan P, et al. Anti-inflammatory effects of Edaravone and Scutellarin in activated microglia in experimentally induced ischemia injury in rats and in BV-2 microglia[J]. BMC neuroscience, 2014, 15(1): 1.
21 Liesz A, Dalpke A, Mracsko E, et al. DAMP signaling is a key pathway inducing immune modulation after brain injury [J]. The Journal of Neuroscience, 2015, 35(2): 583-598.
22 邢鸣,魏民,张鹏,等.依达拉奉联合尼莫地平治疗颅脑外伤的效果观察[J].临床神经外科杂志,2014,27(6):468-470.