

中图分类号: R969.4 文献标志码: A 文章编号: 1006-4931(2024)06-0098-04
doi:10.3969/j.issn.1006-4931.2024.06.022



依达拉奉右苄醇联合甘露醇对初诊急性前循环大面积脑梗死继发脑水肿患者神经功能的影响*

常 勇, 李 莉, 陈 琳, 曾超胜[△]

(海南医学院第二附属医院, 海南 海口 570311)

摘要:目的 探讨依达拉奉右苄醇联合甘露醇对初诊急性前循环大面积脑梗死(MCI)继发脑水肿患者神经功能的影响。方法 选取医院神经内科2021年1月至2022年12月收治的MCI继发脑水肿患者110例,按随机数字表法分为观察组和对照组,各55例。两组患者均接受血管内介入取栓联合去骨瓣减压手术及常规抗血小板聚集、抗感染等对症治疗,并予甘露醇注射液静脉滴注,观察组患者加用依达拉奉右苄醇注射液用浓溶液静脉滴注。两组均连续治疗15 d。结果 观察组总有效率为83.64%,显著高于对照组的65.45% ($P < 0.05$)。与对照组比较,观察组患者治疗后的脑水肿体积显著缩小,美国国立卫生研究院卒中量表(NIHSS)评分及改良Rankin量表(mRS)评分均显著降低($P < 0.05$),血清神经元特异性烯醇化酶、S100钙结合蛋白 β 、肿瘤坏死因子- α 及白细胞介素 1β 水平均显著降低($P < 0.05$)。观察组与对照组不良反应发生率无显著差异(7.27%比12.73%, $P > 0.05$)。结论 依达拉奉右苄醇联合甘露醇治疗初诊急性前循环MCI继发脑水肿,能明显缩小脑水肿体积,改善神经功能,抑制炎症反应。

关键词:依达拉奉右苄醇;甘露醇;初诊;急性脑梗死;前循环;大面积脑梗死;脑水肿;神经功能;炎症反应

Effects of Edaravone and Dexborneol Combined with Mannitol on the Neurological Function in Patients with Newly - Diagnosed Cerebral Edema Secondary to Acute Anterior - Circulation Massive Cerebral Infarction

CHANG Yong, LI Li, CHEN Lin, ZENG Chaosheng

(The Second Affiliated Hospital of Hainan Medical University, Haikou, Hainan, China 570311)

Abstract: Objective To investigate the effects of edaravone and dexborneol combined with mannitol on the neurological function in patients with newly - diagnosed cerebral edema secondary to acute anterior - circulation massive cerebral infarction (MCI).

*基金项目:海南省重点研发项目[ZDYF2022SHFZ291]。

第一作者:常勇,男,大学本科,住院医师,研究方向为脑血管病的诊治,(电子信箱)cy19942023@163.com。

[△]通信作者:曾超胜,男,大学本科,主任医师,研究方向为神经重症医学,(电子信箱)Zengchaosheng176@sina.com。

- Biomarkers in acute kidney injury - pathophysiological basis and clinical performance[J]. Acta Physiol (Oxf), 2017, 219(3): 554 - 572.
- [9] KELLUM JA, LAMEIRE N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary [J]. Critical Care, 2013, 17(1): 204.
- [10] SLIMANI M. Incidence and predictive factors of contrast induced nephropathy in cardiac patients undergoing coronary angiography. Experience of the cardiology department, in a cohort of 746 patients[J]. Archives of Cardiovascular Diseases Supplements, 2021, 13(1): 168 - 169.
- [11] GORELIK Y, BLOCH - ISENBERG N, HEYMAN SN, et al. Renal Functional Recovery Confounding the Assessment of Contrast Nephropathy: Propensity Score Analysis [J]. American Journal of Nephrology, 2021, 52(1): 1 - 8.
- [12] DAVENPORT MS, PERAZELLA MA, YEE J, et al. Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation[J]. Radiology, 2020, 294(3): 660 - 668.
- [13] MA B, ALLEN DW, GRAHAM MM, et al. Comparative Performance of Prediction Models for Contrast - Associated Acute Kidney Injury After Percutaneous Coronary Intervention[J]. Circulation Cardiovascular Quality and Outcomes, 2019, 12(11): 1 - 11.
- [14] TROPEANO F, LEONCINI M, TOSO A, et al. Impact of Rosuvastatin in Contrast - Induced Acute Kidney Injury in the Elderly: Post Hoc Analysis of the PRATO - ACS Trial [J]. J Cardiovasc Pharmacol Ther, 2016, 21(2): 159 - 166.
- [15] 潘汉超. 老年人造影剂相关急性肾损伤的研究进展[J]. 国际泌尿系统杂志, 2020, 40(6): 1143 - 1145.
- [16] 窦鸿伟, 王国位, 陈 亮, 等. 冠状动脉造影术前应用瑞舒伐他汀和阿托伐他汀对老年患者肾功能影响的对比分析[J]. 第二军医大学学报, 2018, 39(12): 1330 - 1335.
- [17] MEHRAN R, AYMONG ED, NIKOLSKY E, et al. A simple risk score for prediction of contrast - induced nephropathy after percutaneous coronary intervention: Development and initial validation[J]. J Am Coll Cardiol, 2004, 44(7): 1393 - 1399.

(收稿日期: 2023 - 04 - 07; 修回日期: 2023 - 07 - 10)

Methods A total of 110 patients with cerebral edema secondary to MCI admitted to the Department of Neurology in the hospital from January 2021 to December 2022 were selected and divided into the observation group and the control group by the random number table method, with 55 cases in each group. The patients in the two groups were given intravascular thrombectomy combined with decompressive craniectomy and symptomatic treatment (such as conventional antiplatelet aggregation, anti-infection) and intravenous drip of Mannitol Injection, on this basis, the patients in the observation group were given intravenous drip of Edaravone and Dexborneol Concentrated Solution for Injection. Both groups were treated continuously for 15 d. **Results** The total effective rate in the observation group was 83.64%, which was significantly higher than 65.45% in the control group ($P < 0.05$). Compared with those in the control group, the volume of cerebral edema, the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores in the observation group significantly decreased after treatment ($P < 0.05$), the neuron-specific enolase (NSE), S100 calcium-binding protein β (S100 β), tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) levels significantly decreased ($P < 0.05$). The incidence of adverse reactions in the observation group was similar to that in the control group (7.27% vs. 12.73%, $P > 0.05$). **Conclusion** Edaravone and dexborneol combined with mannitol can obviously decrease the volume of cerebral edema, improve neurological function, and inhibit inflammatory reaction in patients with newly-diagnosed cerebral edema secondary to acute anterior-circulation MCI.

Key words: edaravone and dexborneol; mannitol; newly-diagnosed; acute cerebral infarction; anterior-circulation; massive cerebral infarction; cerebral edema; neurological function; inflammatory reaction

大面积脑梗死(MCI)占脑梗死病例总数的2%~8%^[1],病情严重,且预后差,致死率和致残率均较高,MCI后继发脑水肿是导致预后不良的重要原因,水肿压迫病灶周围神经,对脑组织造成二次损伤,增加昏迷、脑疝及死亡风险^[2]。MCI继发脑水肿风险较高,积极预防和控制脑水肿是MCI临床治疗的重点和难点^[3]。甘露醇为降低颅内压的常用药物,可促进脑组织脱水,减轻脑水肿程度,但大量使用易引起电解质紊乱和肾损害等,影响疗效^[4]。依达拉奉右莰醇为新型脑保护剂,具有抗氧化、修复神经功能的作用^[5-6],用于脑梗死的疗效已获证实,但目前对于MCI继发脑水肿效果的报道较少。鉴于此,本研究中探讨了两药联合治疗初诊急性前循环MCI继发脑水肿的效果,并分析其对患者神经功能、炎症指标的影响。现报道如下。

1 资料与方法

1.1 一般资料

纳入标准:符合急性前循环MCI的诊断标准^[7];发病48 h内病情恶化,并出现脑水肿^[8];首次发病;接受血管内介入取栓联合去骨瓣减压手术。本研究经医院医学伦理委员会批准(伦理批号:hney2021-011),患者及其家属均签署知情同意书。

排除标准:合并脑出血或有出血倾向;陈旧性脑血管病灶、脑动脉瘤、脑肿瘤及混合型脑卒中;生命体征不稳定;心、肝、肾等脏器功能异常;合并恶性肿瘤、血液疾病、感染性疾病或其他影响研究结果的疾病;既往认知障碍或精神性疾病;对本研究拟用药物过敏,不积极配合治疗;转院或转科室治疗;临床资料不全。

病例选择与分组:选取医院神经内科2021年1月至2022年12月收治的MCI继发脑水肿患者110例,按

表1 两组患者一般资料比较($n = 55$)

Tab. 1 Comparison of the patients' general data between the two groups ($n = 55$)

组别	性别 (男/女,例)	年龄 ($\bar{X} \pm s$,岁)	体质量指数 ($\bar{X} \pm s$,kg/m ²)	发病至治疗时间 ($\bar{X} \pm s$,h)
观察组	31/24	61.63 $\pm$ 6.43	21.73 $\pm$ 1.72	9.25 $\pm$ 2.66
对照组	28/27	60.81 $\pm$ 6.15	21.89 $\pm$ 1.67	8.97 $\pm$ 2.13
χ^2/t 值	0.329	0.728	0.516	0.663
P 值	0.566	0.468	0.607	0.509

随机数字表法分为观察组和对照组,各55例。两组患者一般资料比较,差异无统计学意义($P > 0.05$),具有可比性。详见表1。

1.2 方法

两组患者均接受血管内介入取栓联合去骨瓣减压手术,以及常规抗血小板聚集、抗感染、维持酸碱平衡、控制血糖、降血压等对症治疗,同时予甘露醇注射液(四川国瑞药业有限责任公司,国药准字H51020055,规格为每瓶250 mL:50 g)250 mL静脉滴注,每日3次。观察组患者加予依达拉奉右莰醇注射用浓溶液(海南先声药业有限公司,国药准字H20200007,规格为每支5 mL:依达拉奉10 mg与右莰醇2.5 mg)10 mL静脉滴注,每日1次。两组均连续治疗15 d。

1.3 观察指标与疗效判定标准

观察指标:1)脑水肿体积。患者行头颅CT检查,测量脑水肿边缘范围,计算脑水肿体积。脑水肿体积(cm³)=长(cm)×宽(cm)×层厚(cm)×层数×($\pi/6$)。2)实验室指标。采集患者治疗前后的外周静脉血各4 mL,3 500 r/min离心15 min,分离血清,采用酶联免疫吸附法测定血清神经功能指标[神经元特异性烯醇化酶

(NSE)、S100钙结合蛋白 β (S100 β)及炎性指标[肿瘤坏死因子- α (TNF- α)、白细胞介素1 β (IL-1 β)]水平。
3)量表评分。采用美国国立卫生研究院卒中量表(NIHSS)和改良Rankin量表(mRS)评估患者的神经功能,均为分值越高表明症状越严重。

疗效判定^[9]:显效,NIHSS评分降幅>80%,且CT或磁共振(MRI)示脑水肿基本消失;有效,NIHSS评分降幅为45%~79%,CT或MRI示脑水肿周围呈低密度影;无效,未达到以上标准。总有效=显效+有效。

安全性:统计患者治疗过程中胃肠道反应、出血、皮疹、肝功能异常等不良反应发生情况。

1.4 统计学处理

采用SPSS 22.0统计学软件分析。计量资料以 $\bar{X} \pm s$ 表示,行 t 检验;计数资料以率(%)表示,行 χ^2 检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

结果见表2至表5。

3 讨论

MCI是颈内动脉主干、大脑中动脉或皮质支完全闭塞

表2 两组患者临床疗效比较[例(%), $n = 55$]

Tab. 2 Comparison of clinical efficacy between the two groups
[case (%), $n = 55$]

组别	显效	有效	无效	总有效
观察组	19(34.55)	27(49.09)	9(16.36)	46(83.64)
对照组	14(25.45)	22(40.00)	19(34.55)	36(65.45)
χ^2 值				4.791
P 值				0.029

表3 两组患者脑水肿体积与量表评分比较($\bar{X} \pm s$, $n = 55$)

Tab. 3 Comparison of cerebral edema volume, NIHSS and mRS scores between the two groups ($\bar{X} \pm s$, $n = 55$)

组别	脑水肿体积(cm^3)		NIHSS评分(分)		mRS评分(分)	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
观察组	20.13 $\pm$ 3.87	7.37 $\pm$ 1.61 [*]	15.19 $\pm$ 2.99	8.35 $\pm$ 1.67 [*]	3.04 $\pm$ 0.73	1.44 $\pm$ 0.31 [*]
对照组	20.45 $\pm$ 4.06	11.87 $\pm$ 2.21 [*]	15.76 $\pm$ 3.06	9.46 $\pm$ 1.85 [*]	3.12 $\pm$ 0.71	1.91 $\pm$ 0.49 [*]
t 值	0.406	12.197	1.190	3.136	0.576	3.716
P 值	0.685	0.000	0.237	0.002	0.566	0.000

注:与本组治疗前比较,* $P < 0.05$ 。表4同。

Note: Compared with those before treatment, * $P < 0.05$ (for Tab. 3 - 4).

表4 两组患者神经功能和炎性因子水平比较($\bar{X} \pm s$, $n = 55$)

Tab. 4 Comparison of neurological function and inflammatory factor levels between the two groups ($\bar{X} \pm s$, $n = 55$)

组别	NSE($\mu\text{g/L}$)		S100 β ($\mu\text{g/L}$)		TNF- α (ng/L)		IL-1 β (pg/mL)	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
观察组	20.66 $\pm$ 3.29	9.35 $\pm$ 1.31 [*]	0.81 $\pm$ 0.14	0.43 $\pm$ 0.08 [*]	31.12 $\pm$ 5.23	16.14 $\pm$ 3.24 [*]	19.56 $\pm$ 3.83	9.23 $\pm$ 1.46 [*]
对照组	21.04 $\pm$ 3.16	12.53 $\pm$ 1.65 [*]	0.83 $\pm$ 0.15	0.55 $\pm$ 0.09 [*]	31.85 $\pm$ 5.51	22.04 $\pm$ 3.75 [*]	19.74 $\pm$ 3.58	12.92 $\pm$ 2.06 [*]
t 值	0.596	10.480	0.257	7.004	0.652	10.295	0.296	10.222
P 值	0.552	0.000	0.798	0.000	0.5116	0.000	0.768	0.000

表5 两组患者不良反应发生情况比较[例(%), $n = 55$]

Tab. 5 Comparison of the incidence of adverse reactions between the two groups [case (%), $n = 55$]

组别	胃肠道反应	出血	皮疹	肝功能异常	合计
观察组	2(3.64)	0(0)	2(3.64)	0(0)	4(7.27)
对照组	3(5.46)	1(1.82)	2(3.64)	1(1.82)	7(12.73)
χ^2 值					0.909
P 值					0.340

造成的大范围梗死,其发病急、病情严重,且预后不佳,急性期病死率高达5%~15%^[10]。MCI继发的缺血性脑水肿是影响预后的关键因素,预防和改善脑水肿程度对于MCI的治疗尤为重要^[11-12]。

依达拉奉右莰醇是治疗缺血性脑血管疾病的药物,具有保护、修复神经的双重作用。且能清除多种自由基、抗细胞凋亡,有助于改善脑缺血症状^[13]。XU等^[14]的研究发现,该药治疗急性脑梗死的效果较依达拉奉更佳,可有效改善预后和日常生活能力。有研究表明,依达拉奉右莰醇能通过激活核因子E2相关

因子2/血红素加氧酶-1(Nrf2/HO-1)途径达到抗氧化、抗炎作用,抑制神经细胞凋亡,改善模型小鼠脑缺血引起的记忆功能减退^[15]。本研究结果显示,观察组总有效率显著高于对照组,且观察组患者治疗后的NIHSS评分、mRS评分显著低于对照组,脑水肿体积显著小于对照组,提示依达拉奉右莰醇效果显著,可有效减轻水肿程度,促进神经功能恢复,改善日常生活能力。依达拉奉右莰醇具有多靶点协同作用,其有效成分中的依达拉奉可清除缺血带周围的过量自由基,抑制细胞凋亡,保护和修复神经功能,加速解除脑水肿占位;右莰醇则可调节 γ -氨基丁酸受体,抑制谷氨酸毒性作用,减少脑神经细胞损害,发挥保护神经功能的作用。

NSE和S100 β 是神经功能损害的重要标志物,正常情况下血液NSE和S100 β 含量较低,脑梗死发病导致脑组织缺氧,脑细胞凋亡坏死,NSE和S100 β 等神经因子被大量释放,导致其水平升高。本研究结果发现,两组患者治疗后的血清NSE和S100 β 水平均显著降低,且观

察组血清NSE和S100 β 水平低于对照组,证实依达拉奉右莰醇能进一步降低神经损伤程度,减少神经因子释放。依达拉奉右莰醇具有抗氧化作用,可有效清除自由基,抑制神经过氧化损害,与脱水剂联用达到协同增效作用,可抑制脑水肿程度,降低颅内压,减轻脑组织损害,从而保护神经功能,提高临床疗效。

炎症反应在脑水肿病理过程中起着关键作用,MCI导致脑组织受损,炎症反应被激活,炎症因子过量表达;过度炎症反应又会加剧血-脑脊液屏障破坏,促进脑水肿的发生和发展^[16]。TNF- α ,IL-1 β 等炎症因子在脑损伤过程中发挥重要作用,可作为评价脑损伤程度和判断预后的参考指标^[17-18]。本研究结果显示,两组患者治疗后的血清TNF- α 和IL-1 β 水平降低,且观察组低于对照组,提示依达拉奉右莰醇能进一步改善机体的炎症反应。依达拉奉右莰醇可清除自由基,抑制核因子- κ B信号通路,改善氧化应激和炎症反应,抑制炎症因子的产生,从而促进神经功能恢复。本研究的不足为样本量较小,随访时间也较短,有待后续研究改进。

综上所述,依达拉奉右莰醇联合甘露醇治疗初诊急性前循环MCI继发脑水肿,能有效抑制脑水肿程度,减轻炎症反应,促进神经功能的恢复。

参考文献

- [1] SEHWEIL SMM, GONCHAROVA ZA. How I do it: decompressive hemicraniectomy supplemented with resection of the temporal pole and tentoriotomy for malignant ischemic infarction in the territory supplied by the middle cerebral artery[J]. Acta Neurochir (Wien), 2022, 164(6): 1653-1657.
- [2] NG FC, YASSI N, SHARMA G, et al. Cerebral edema in patients with large hemispheric infarct undergoing reperfusion treatment: a HERMES meta-analysis[J]. Stroke, 2021, 52(11): 3450-3458.
- [3] LU H, ASHIQUEALI R, LIN CI, et al. Histone deacetylase 3 inhibition decreases cerebral edema and protects the blood-brain barrier after stroke[J]. Mol Neurobiol, 2023, 60(1): 235-246.
- [4] 罗志中, 王鑫, 冯凯. 甘露醇对心脏骤停模型大鼠心肺复苏后脑水肿及大脑中动脉血流的影响[J]. 中国药业, 2021, 30(11): 40-43.
- [5] 朱娴, 陈薪旭, 陈奕斌, 等. 依达拉奉右莰醇联合血管内介入治疗对MCI患者血清NSE、S100 β 、ROS、NO、MDA及GSH-px水平的影响[J]. 脑与神经疾病杂志, 2023, 31(6): 363-366.
- [6] HU RY, LIANG J, DING L, et al. Edaravone dextrorotatory provides neuroprotective benefits by suppressing NLRP3 inflammasome-induced microglial pyroptosis in experimental ischemic stroke[J]. Int Immunopharmacol, 2022, 113(Pt A): 109315.
- [7] 中华医学会神经外科学分会, 国家卫健委脑卒中筛查与防治工程委员会, 海峡两岸医药卫生交流协会神经外科分会缺血性脑血管病学组. 大面积脑梗死外科治疗指南[J]. 中华医学杂志, 2021, 101(45): 3700-3711.
- [8] 中华医学会神经外科学分会, 中国神经外科重症管理协作组, 中国神经外科转化与循证医学协作组, 等. 高渗盐水治疗脑水肿及颅内高压的专家共识[J]. 中华医学杂志, 2022, 102(17): 1258-1266.
- [9] 中华医学会神经病学分会, 中华医学会神经病学分会神经康复学组, 中华医学会神经病学分会脑血管病学组. 中国脑卒中早期康复治疗指南[J]. 中华神经科杂志, 2017, 50(6): 405-412.
- [10] SARRAJ A, HASSAN AE, ABRAHAM MG, et al. Trial of endovascular thrombectomy for large ischemic strokes[J]. N Engl J Med, 2023, 388(14): 1259-1271.
- [11] 朱亮, 衡卫卫, 王江波. 依达拉奉联合尼莫地平对大面积脑梗死患者神经功能和血氧状态的影响[J]. 中国药业, 2018, 27(10): 48-50.
- [12] FERRO D, MATIAS M, NETO J, et al. Neutrophil-to-lymphocyte ratio predicts cerebral edema and clinical worsening early after reperfusion therapy in stroke[J]. Stroke, 2021, 52(3): 859-867.
- [13] ZHANG XL, LIU Y, CHENG X, et al. Effect of edaravone dextrorotatory on the serum levels of lipoprotein-related phospholipase A2 and high-sensitivity C-reactive protein in patients with acute cerebral infarction[J]. Asian J Surg, 2023, 46(3): 1420-1421.
- [14] XU J, WANG A, MENG X, et al. Edaravone dextrorotatory versus edaravone alone for the treatment of acute ischemic stroke: a phase III, randomized, double-blind, comparative trial[J]. Stroke, 2021, 52(3): 772-780.
- [15] XU L, GAO Y, HU M, et al. Edaravone dextrorotatory protects cerebral ischemia reperfusion injury through activating Nrf2/HO-1 signaling pathway in mice[J]. Fundam Clin Pharmacol, 2022, 36(5): 790-800.
- [16] IBRAHIM F, MENEZES S, BUHNERKEMPE M, et al. Systemic white blood cell count as a biomarker for malignant cerebral edema in large vessel ischemic MCA stroke[J]. J Stroke Cerebrovasc Dis, 2022, 31(8): 106550.
- [17] LI W, LIU D, XU J, et al. Astrocyte-derived TNF- α -activated platelets promote cerebral ischemia/reperfusion injury by regulating the RIP1/RIP3/AKT signaling pathway[J]. Mol Neurobiol, 2022, 59(9): 5734-5749.
- [18] KAO MH, WU JS, CHEUNG WM, et al. Clinacanthus nutans mitigates neuronal death and reduces ischemic brain injury: role of NF- κ B-driven IL-1 β transcription[J]. Neuromolecular Med, 2021, 23(1): 199-210.

(收稿日期: 2023-08-27; 修回日期: 2023-11-30)