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丁苯酞软胶囊对急性脑梗死患者ROS、T-AOC、炎症因子及神经功能的影响

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摘要 目的：探讨丁苯酞软胶囊对急性脑梗死患者活性氧(reactive oxygen species, ROS)、总抗氧化能力(total antioxidant capacity, T-AOC)、炎症因子及神经功能的影响。**方法：**将2016年7月至2017年7月我院收治的急性脑梗死患者100例随机分为对照组(n=50)和观察组(n=50)。对照组患者给予常规对症治疗，观察组患者在对照组的基础上加用丁苯酞软胶囊。两组连续治疗14天后，比较治疗前后两组血清ROS、T-AOC、炎症因子水平及神经功能的变化及治疗后两组的临床疗效。**结果：**治疗前，两组血清ROS、T-AOC、高敏C反应蛋白(high sensitive C reaction protein, hs-CRP)、肿瘤坏死因子-α(tumor necrosis factor, TNF-α)、白细胞介素-6(interleukin-6, IL-6)水平、美国国立卫生研究院卒中量表(National Institute of Health stroke scale)评分比较差异均无统计学意义(P>0.05)。与本组治疗前比较，两组治疗后血清T-AOC水平显著升高，且观察组显著高于对照组(P<0.05)；对照组治疗后血清ROS水平显著高于治疗前(P<0.05)，观察组患者治疗前后的血清ROS水平相比差异无统计学意义(P>0.05)，且观察组治疗后ROS水平显著低于对照组(P<0.05)；两组血清hs-CRP、TNF-α、IL-6水平、NHISS评分均显著低于治疗前(P<0.05)，且观察组以上指标均显著低于对照组(P<0.05)；观察组总有效率为82%，明显优于对照组的52%(P<0.05)。**结论：**在常规治疗的基础上加用丁苯酞软胶囊可有效降低急性脑梗死患者血清炎症因子水平，提高机体总抗氧化能力，促进神经功能的修复，提高临床治疗效果

关键词：丁苯酞；急性脑梗死；活性氧；总抗氧化能力；炎症因子；NHISS评分

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Effect of Butylphthalide Soft Capsules on the ROS, T-AOC, Inflammatory Factors and Neurological Function of Patients with Acute Cerebral Infarction

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ABSTRACT Objective: To investigate the effects of butylphthalide soft capsules on the generation of ROS, T-AOC, inflammatory factors, and neurological function of patients with acute cerebral infarction. **Methods:** 100 cases of acute cerebral infarction patients in our hospital were randomly divided into the control group (n=50) and the observation group (n=50), patients in the control group was given conventional thraphy, whie the observation group was treated with butylphthalide soft capsules based on the control group. Both groups were given sustainable treatment for 14 days, the levels of serum ROS, T-AOC, inflammatory factors and neurological function were compared before and after treatment. **Results:** The levels of ROS, T-AOC, hs-CRP, TNF-α, IL-6, NHISS score in both groups showed no statistically significant difference before treatment (P>0.05). Compared with before treatment, the T-AOC levels of both groups were significantly increased after treatment (P<0.05), and which was significantly higher in the observation group than that of the control group after treatment (P<0.05); the ROS level in control group was significantly higher after treatment than that in the same group before treatment (P<0.05), which showed no significant difference in the observation group before and after treatment, and the level of ROS in the observation group was significantly lower than that in the control group after treatment (P<0.05). After treatment, the levels of serum hs-CRP, TNF-α, IL-6 and NHISS score in the two groups were significantly lower than those in the same group before treatment (P<0.05), the above indexes in the observation group were significantly lower than those in the control group (P<0.05). The total effective rate was 82% in the observation group, which was significantly better than 52% in the control group (P<0.05). **Conclusion:** On the basis of conventional treatment, the addition of butylphthalide soft capsules could effectively reduce the levels of serum inflammatory factors and ROS, improve the total antioxidant capacity, promote the recovery of neurological function.

Key words: Butylphthalide; Acute cerebral infarction; Reactive oxygen species; Total antioxidant capacity; Inflammatory factors; NHISS score

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前言

急性脑梗死(Acute cerebral infarct, ACI)是指脑部血液供应突然中断而导致的脑组织坏死,是神经内科常见疾病[1,2]。该病既往多发于老年人群,但近年来,随着我国逐步步入老龄化社会及人民生活水平的提高,其发病率不断攀升,且发病年龄有提前的趋势,已成为威胁我国国民健康康的重大疾病[3,4]。临床相关研究表明氧化应激损伤、炎症反应及神经功能缺损与 ACI 的发生发展密切相关,控制患者体内上述指标变化有助于降低患者致残率和病死率,促进患者尽快康复[5-7]。丁苯酞注射液是一类新型神经保护药物,在改善患者缺血区脑灌注和神经功能缺损方面效果显著[8,9]。因此,本研究主要探讨了丁苯酞软胶囊对 ACI 患者体内氧化应激损伤、炎症因子及神经功能的影响,旨在为 ACI 临床治疗提供新的线索。

1 对象与方法

1.1 研究对象

选取 2016 年 7 月至 2017 年 7 月我院收治的急性脑梗死患者 100 例作为研究对象。所有对象均符合本研究筛选标准。纳入标准:① 符合中国急性缺血性脑卒中诊治指南制定的诊断标准(2010 版)[10];② 发病时间小于 72 小时;③ 梗死部位经 MRI 或头部 CT 证实;④ 发病年龄小于 80 岁;⑤ 所有研究对象及家属均知情同意,签署知情同意书并自愿加入治疗。排除标准:① 患有严重心血管疾病、肝肾功障碍、恶性肿瘤者;② 患有免疫性及感染性疾病者;③ 伴有其他颅内病变者;④ 多脏器功能衰竭患者;⑤ 未能按疗程完成治疗,中途脱落病例,且入院时临床资料不全者。所有患者依据随机数据表法分为对照组(n=50)和观察组(n=60)。对照组中,男性 23 例,女性 27 例,年龄 40~78 岁;观察组中,男性 28 例,女性 22 例,年龄 42~79 岁。两组患者年龄、性别等一般资料方面比较差异均无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组患者给予常规治疗,具体方法如下:口服阿司匹林 100 mg,阿托伐他汀钙 20 mg,每天 1 次;静脉滴注小牛血清去蛋白注射液 0.8 g,疏血通注射液 6 mL,每天 1 次,并控制血压、血糖等危险因素,维持患者的水、电解质平衡,连续治疗 14 天。观察组在此基础上加用丁苯酞软胶囊,200 mg/ 次, 每天 3 次,连续治疗 14 天。

1.3 指标检测

分别于治疗前后抽取两组患者静脉血 10 mL,置普通试管中静置几分钟,随后 3000 r/min,离心 10 min,收集上清于 EP 管中,放置在 -20 ℃冰箱中待测。① 血清炎症因子的检测:TNF-α 的检测采用放射免疫法, 试剂盒购于上海恒远生物公司;hs-CRP 的检测采用乳胶增强免疫透射比浊法, 试剂盒由上海睿康生物科技有限公司提供;IL-6 的检测采用酶联免疫法,试剂盒购自上海超研生物科技有限公司。② 采用 Fenton 法测定 ROS 水平试剂盒购于上海生物工程有限公司,测定方法严格按照说明书进行;采用 T-AOC 检测试剂盒测定 T-AOC 水平(试剂盒购于上海生物工程有限公司), 使用紫外分光光度仪,520 nm 波长测定 OD 值。总抗氧化能力 = (测定 OD 值 - 对照 OD 值)/ 0.01/ 30× (反应液总量 / 取样量)× 样本稀释倍数。

1.4 疗效评定

基本治愈:与治疗前相比,NIHSS 评分降低 91%-100%,病残程度 0 级,体征及症状消失;显效:与治疗前相比,NIHSS 评分降低 46%-90%, 病残程度 1-3 级, 体征及症状显著减轻;有效:与治疗前相比,NIHSS 评分降低 18%-45%,体征及症状稍微出现好转;无效:与治疗前相比,NIHSS 评分降低小于 17%,体征及症状无明显好转。临床有效率为基本治愈与显效占总例数的百分比。

1.5 神经功能损伤评定

脑梗死病人神经功能损伤情况采用 NIHSS 量表评定,NIHSS 量表共包括面瘫、意识、走路、语言、四肢肌力等 15 个项目,得分越高表明病人的神经功能缺损程度越严重。

1.6 统计学分析

研究所得数据选用 SPSS22.0 软件进行统计分析, 计数资料以($\bar{x}\pm s$)表示,组内及组间各指标比较采用 t 检验,计数资料以百分比表示并采用 x^2 检验,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组治疗前后血清 T-AOC、ROS 水平比较

如表 1 所示,两组治疗前血清 T-AOC、ROS 水平比较差异无统计学意义(P>0.05)。治疗后,对照组与观察组 T-AOC 水平分别为(10.02± 1.17)U/mL 和(11.52± 1.19)U/mL,均较治疗前显著升高,且观察组显著高于对照组,差异有统计学意义(P<0.05);治疗后,对照组血清 ROS 水平显著高于同组治疗前,差异有统计学意义(P<0.05),观察组患者治疗前后的血清 ROS 水平相比,差异不显著(P>0.05),且观察组治疗后血清 ROS 水平显著低于对照组(P<0.05)。

表 1 两组治疗前后血清 T-AOC、ROS 水平的比较($\bar{x}\pm s$)

Table 1 Comparison of the serum Levels of T-AOC, ROS between two groups before and after treatment($\bar{x}\pm s$)

Group	Cases	Time	T-AOC(U/mL)	ROS(U/mL)
Control group	50	Before treatment	9.96± 0.81	536.32± 28.39
		After treatment	10.02± 1.17*	556.62± 19.29*
Observation group	50	Before treatment	9.95± 0.83	536.82± 28.91
		After treatment	11.52± 1.19*#	539.67± 29.15#

Note: compared with pre-treatment in the same group, *P<0.05;compared with post-treatment in the control group, #P<0.05.

2.2 两组治疗前后血清炎症因子水平的比较

如表 2 所示,两组治疗前血清 hs-CRP、TNF-α、IL-6 水平比

较差异均无统计学意义 (P>0.05)。治疗后，对照组与观察组 hs-CRP、TNF-α、IL-6 水平分别为 (6.45± 0.94)mg/L、(30.41± 5.31)μg/L、(10.16 ± 2.52)ng/L 和 (3.98 ± 1.12)mg/L、(21.62 ± 4.29)μg/L、(7.82± 2.46)ng/L，均较本组治疗前显著降低，且观察组以上指标均显著低于对照组(P<0.05)。

表 2 两组治疗前后血清炎症因子水平的比较($\bar{x}$± s)

Table 2 Comparison of the serum Levels of inflammatory cytokines between two groups before and after treatment($\bar{x}$± s)

Group	Cases	Time	hs-CRP(mg/L)	TNF-α(μg/L)	IL-6(ng/L)
Control group	50	Before treatment	12.76± 1.30	48.82± 8.89	14.03± 2.98
		After treatment	6.45± 0.94*	30.41± 5.31*	10.16± 2.52*
Observation group	50	Before treatment	12.82± 1.28	49.77± 8.56	13.99± 3.01
		After treatment	3.98± 1.12*#	21.62± 4.29*#	7.82± 2.46*#

Note: compared with pre-treatment in the same group, *P<0.05; compared with post-treatment in the control group, #P<0.05.

2.3 两组治疗前后 NHISS 评分的比较

如表 3 所示，两组治疗前 NHISS 评分比较差异均无统计学意义(P>0.05)。治疗后，对照组与观察组 NHISS 评分分别为 (5.29± 2.17)、(4.26± 1.92)，均较本组治疗前显著降低，且观察组显著低于对照组，差异有统计学意义(P<0.05)。

表 3 两组治疗前后 NHISS 评分的比较($\bar{x}$± s)

Table 3 Comparison of the NHISS score between the two groups before and after treatment($\bar{x}$± s)

Group	Cases	NHISS Score(Score)	
		Before treatment	After treatmen
Control group	50	10.95± 4.35	5.29± 2.17*
Observation group	50	10.74± 4.29	4.26± 1.92*#

Note: compared with pre-treatment in the same group, *P<0.05; compared with post-treatment in the control group, #P<0.05.

2.4 两组临床疗效的比较

治疗后，观察组总有效率为 82%(41 例)，明显高于对照组的 52%(26 例)，差异有统计学意义(P<0.05)，见表 4。

表 4 两组治疗后临床疗效的比较[例(%)]

Table 4 Comparison of the clinical efficacy between two groups after treatment($\bar{x}$± s)

Group	Cases	Basic cure	excellence	Effective	Invalid	The total efficiency
Control group	50	14	12	16	8	26(52%)
Observation group	50	26	15	6	3	41(82%*)

Note: compared with the control group, *P<0.05.

3 讨论

ACI 发病机制复杂，其公认的危险因素包括高血压病、糖尿病、吸烟、饮酒、肥胖等。患者发病时可出现言语不利和肌力下降，严重者可导致患者意识障碍甚至危及患者生命[11-13]。因此，采取积极有效的药物治疗对患者十分重要。丁苯酞为人工合成的消旋正丁基苯酞，与天然的左旋芹菜甲素的结构相同，是近年来研发的治疗 ACI 疾病的新型药物[14-16]。临床研究结果显示丁苯酞可改善 ACI 患者中枢神经功能的损伤，有助于患者神经功能损伤后恢复[17]。现代药理学证实丁苯酞可阻断因脑梗死所引起的脑损伤的多个病理环节，具有很强的抗脑缺血作用，同时可明显减少因局部脑缺血所致的梗塞面积，减轻脑水肿，改善缺血脑区的血液循环和脑部能量代谢，抑制神经元细胞凋亡，改善神经功能损伤状况，并且具有抑制血小板聚集和抗脑血栓形成的作用[18-20]。

脑梗死发生后，脑部缺氧缺血造成线粒体 DNA(mtDNA)及呼吸链损伤，线粒体电子传递链功能发生障碍，产生大量的氧自由基。氧自由基的大量增加及线粒体功能障碍最终导致神经元细胞凋亡[21-23]。因此，线粒体结构和功能的保护也成为了脑梗死疾病治疗的关键。本研究显示两组治疗后 T-AOC 水平均较治疗前显著升高，且观察组显著高于对照组，而观察组治疗后血清 ROS 水平显著低于对照组治疗后，表明丁苯酞软胶囊对线粒体具有一定的抗氧化损伤作用，可抑制 ROS 的生成，并能够提高机体 T-AOC 能力，减少细胞凋亡。这可能与丁苯酞有助于提高 Ca^{2+}-Mg^{2+}-ATP 酶、Na^{+}-K^{+}-ATP 酶和超氧化物歧化酶的活性，从而阻止氧化酶的激活和防止脂质过氧化有关[24]。

研究表明 ACI 的发生发展与机体局部或全身炎症反应密切有关，并且炎症反应贯穿 ACI 发生、发展的全过程。目前，通常以 hs-CRP、TNF-α、IL-6 等细胞因子作为 ACI 的炎症标记物[25,26]。hs-CRP 是由肝细胞合成的一种急相期蛋白，可通过诱导炎症因子的分泌，增加粥样硬化斑块的不稳定性，造成血栓和栓塞形成。因此，检测其浓度对 ACI 的干预及预后起重要作用

[27]。TNF-α是主要由单核-巨噬细胞分泌的炎性因子,可通过诱导网络级联反应、诱导细胞凋亡、破坏血脑屏障等途径加重脑缺血神经损伤[28]。IL-6是一种多功能炎性因子,可刺激肝细胞产生急相期蛋白,参与炎症反应,与hs-CRP、TNF-α以网络级联形式在脑缺血神经损伤中发挥作用[29]。当脑部出现大面积梗死时,患者的体内血清CRP、TNF-α、IL-6水平将会出现明显变化。本研究结果显示:经丁苯酞治疗后,患者血清hs-CRP、TNF-α、IL-6水平显著降低,且明显低于对照组,表明丁苯酞能够降低患者的血清炎性因子水平,其原因可能与丁苯酞通过抑制细胞内钙超载,降低细胞内花生四烯酸含量,抑制炎症因子表达,抑制氧自由基的释放和细胞凋亡,减轻脑水肿等有关。此外,两组NHISS评分均较治疗前显著降低,且观察组显著低于对照组。在临床效果方面,观察组总有效率明显优于对照组,提示在常规治疗的基础上加用丁苯酞软胶囊治疗急性脑梗死,能明显改善患者神经功能缺损情况,控制病情恶化,疗效显著。其原因可能是加用丁苯酞软胶囊治疗后可进一步改善脑部微循环及脑能量代谢,减轻脑组织损伤,保护并修复神经元细胞损伤,改善神经功能,最终提高临床治疗效果[30]。

综上所述,在常规治疗的基础上加用丁苯酞软胶囊可有效降低急性脑梗死患者血清炎症因子水平,提高机体总抗氧化能力,促进神经功能的修复,提高临床治疗效果。

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