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# 康复训练联合神经营养治疗对脑外伤患者康复期神经细胞因子分泌及氧化应激反应的影响

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**[摘要]** **目的:**探讨康复训练联合神经营养治疗对脑外伤患者康复期神经细胞因子分泌及氧化应激反应的影响。**方法:**收集2013年7月~2016年9月间在本院接受治疗的脑外伤康复期患者98例,按照随机数表法分为对照组、观察组,各49例,对照组患者接受常规神经营养治疗,观察组患者接受康复训练联合神经营养治疗,对比两组患者干预前后神经细胞因子、氧化应激指标含量的差异。**结果:**干预前,两组患者血清中神经损伤指标、神经营养指标、氨基酸类神经递质、氧化应激指标含量的差异无统计学意义( $P>0.05$ )。干预后,观察组患者血清中神经损伤指标髓鞘碱性蛋白(MBP)、脑红蛋白(NGB)、神经元特异性烯醇化酶(NSE)、S-100B蛋白(S-100B)的含量以及兴奋性氨基酸谷氨酸(Glu)、天冬氨酸(Asp)的含量低于对照组患者( $P<0.05$ ),神经营养指标脑源性神经营养因子(BDNF)、胶质细胞源性神经营养因子(GDNF)的含量以及抑制性氨基酸 $\gamma$ -氨基丁酸(GABA)、甘氨酸(Gly)的含量高于对照组患者( $P<0.05$ );血清中氧化应激指标超氧化物歧化酶(SOD)、过氧化氢酶(CAT)的含量高于对照组患者,丙二醛(MDA)的含量低于对照组患者( $P<0.05$ )。**结论:**康复训练联合神经营养治疗可有效优化脑外伤康复期患者的神经功能,降低全身氧化应激状态。

**[关键词]** 脑外伤康复期;康复训练;神经营养治疗;氧化应激

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## Effect of rehabilitation training combined with neurotrophic therapy on the nerve cytokine secretion and oxidative stress in rehabilitation period of patients with traumatic brain injury

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

**[ABSTRACT]** **Objective:** To study the effect of rehabilitation training combined with neurotrophic therapy on the nerve cytokine secretion and oxidative stress in rehabilitation period of patients with traumatic brain injury. **Methods:** A total of 98 patients in rehabilitation period of traumatic brain injury who were treated in our hospital between July 2013 and September 2016 were collected and divided into control group and observation group according to the random number table method, 49 cases in each group. Control group received regular neurotrophic therapy, and observation group received rehabilitation training combined with neurotrophic therapy. The differences in the contents of nerve cytokines and oxidative stress indexes were compared between the two groups before and after intervention. **Results:** Before intervention, differences in serum levels of nerve injury

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indexes, neurotrophin indexes, amino acid neurotransmitters and oxidative stress indexes were not statistically significant between the two groups of patients ( $P>0.05$ ). After intervention, serum nerve injury indexes MBP, NGB, NSE and S-100B levels as well as excitatory amino acids Glu and Asp levels of observation group were significantly lower than those of control group ( $P<0.05$ ) while neurotrophin indexes BDNF and GDNF levels as well as inhibitory amino acids GABA and Gly levels were significantly higher than those of control group ( $P<0.05$ ); serum oxidative stress indexes SOD and CAT levels were higher than those of control group while MDA level was significantly lower than that of control group ( $P<0.05$ ). **Conclusion:** Rehabilitation training combined with neurotrophic therapy can effectively optimize the nerve function and reduce the systemic oxidative stress state of patients in rehabilitation period of traumatic brain injury.

[KEY WORDS] Rehabilitation period of traumatic brain injury; Rehabilitation training; Neurotrophic therapy; Oxidative stress

脑外伤可导致患者出现不同程度的神经功能损伤,经急诊手术治疗后患者进入康复期,此阶段干预方法的合理与否将直接决定患者的预后及生活质量<sup>[1,2]</sup>。康复期加入外源性神经营养药物是脑外伤患者治疗的疾病方法,有助于损伤神经元功能的恢复、患者语言及肢体功能的提升,但其疗效存在局限性,部分患者仍遗留严重躯体功能障碍。康复训练是在专人辅助下开展的语言及肢体功能训练,可有效增强损伤部位组织的肌力、帮助恢复神经-肌肉反射,其对脑损伤患者神经细胞功能的影响目前备受关注<sup>[3,4]</sup>。本次研究在外源性神经营养药物治疗的基础上加入康复训练,从神经细胞分泌功能、氧化应激状态等方面对其作用进行阐述,以期明确联合治疗的优越性。

## 1 资料与方法

### 1.1 病例资料

选择2013年7月~2016年9月间在本院接受治疗的脑外伤康复期患者98例,患者家属签署知情同意书。按照随机数表法,入组患者被分为对照组、观察组,各49例,对照组中男性26例、女性23例,年龄32~78岁;观察组中男性27例、女性22例,年龄34~75岁。入组患者性别、年龄分布无显著差异( $P>0.05$ ),具有可比性,医院伦理委员会批准此研究实施。

入组标准:(1)明确脑外伤史,顺利完成手术;(2)遗留不同程度智力、肢体功能障碍;(3)脑外伤前各项功能正常;(4)配合康复治疗。排除标准:(1)合并基础性认知功能异常、无法配合康复锻炼内容的实施;(2)伴全身感染性疾病;(3)伴脑血管畸形、脑肿瘤等与脑外伤无关的脑损伤危险因素。

### 1.2 治疗方法

对照组患者接受脑外伤康复期患者常规神经营养治疗,具体如下:神经节苷脂注射液(齐鲁制药有限公司,国药准字H20056782)40 mg,加入250 mL生理盐水中,静脉滴注,1次/d,以4周为1个疗程。

观察组患者在神经营养治疗基础上,加入康复训练,包括肢体康复训练:(1)早期轻微肢体活动:干预人员帮助患者进行肌力被动训练,包括上肢肩外展、外旋,指关节屈曲,下

肢腕关节外旋、膝关节屈曲、踝关节背屈、足趾屈曲等,单个关节每次运动5~10遍,10 min/次,每日3~4次。(2)主动训练:帮助患者进行Bobath握手、桥式运动、起坐及上下肢协调训练。指导患者进行平衡训练、站立、步行,待患者肢体功能进一步康复后锻炼其穿衣、洗脸、漱口等日常生活活动能力。语言康复训练:(1)初步语言能力训练:强化听觉刺激,先进行舌、唇、软腭等运动训练,选择发音转换、听力理解、看图说话等具体训练内容。(2)实用交流能力训练:随患者语言能力提升,与患者进行谈话交流,1次/d,单次持续30 min,连续治疗4周。

### 1.3 观察指标

干预前后,获取两组患者的空腹肘静脉血3~5 mL,加入抗凝剂并低速离心(3 500 r/min,10~15 min)留取上层血清。采用放射免疫法测定血清中神经损伤指标髓鞘碱性蛋白(MBP)、脑红蛋白(NGB)、神经元特异性烯醇化酶(NSE)、S-100B蛋白(S-100B)的含量;采用酶联免疫吸附法测定神经营养指标脑源性神经营养因子(BDNF)、胶质细胞源性神经营养因子(GDNF)的含量;采用电化学发光法测定氨基酸类神经递质谷氨酸(Glu)、天冬氨酸(Asp)、 $\gamma$ -氨基丁酸(GABA)、甘氨酸(Gly)的含量;采用酶联免疫吸附法测定血清中氧化应激指标超氧化物歧化酶(SOD)、过氧化氢酶(CAT)、丙二醛(MDA)的含量。

### 1.4 统计学处理

采用软件SPSS24.0对文中数据进行记录、计算。神经损伤指标、神经营养指标、氨基酸类神经递质、氧化应激指标等计量资料均以均数±标准差表示,组内干预前后比较采用配对 $t$ 检验,组间比较采用成组 $t$ 检验。 $P<0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 神经损伤指标

干预前、干预后4周时,两组患者血清中神经损伤指标MBP(ng/L)、NGB(pg/mL)、NSE(ng/mL)、S-100B(pg/mL)含量的比较如下:干预前,两组患者血清中MBP、NGB、NSE、S-100B的含量无显著性差异( $P>0.05$ );两组患者干预后4周时血清中MBP、NGB、NSE、S-100B的含量均低于干预前( $P<0.05$ ),且观察组患者干预后4周时血清中MBP、NGB、NSE、S-100B的含量低于对照组患者( $P<0.05$ )。见表1。

表1 两组干预前后血清神经损伤指标含量的变化( $n=49, \bar{x} \pm s$ )

组别	时间	MBP	NGB	NSE	S-100B
对照组	干预前	0.93±0.15	314.38±39.75	30.47±4.51	1.64±0.23
	干预后	0.61±0.07*	130.27±16.58*	17.62±2.14*	0.87±0.09*
观察组	干预前	0.92±0.17	315.67±36.88	30.42±4.37	1.63±0.21
	干预后	0.35±0.05* #	59.86±7.15* #	9.08±1.16* #	0.52±0.07* #

注:组内干预前与干预后比较,\*  $P<0.05$ ;干预后观察组与对照组比较,#  $P<0.05$ 。

## 2.2 神经营养指标

干预前及干预后4周时,两组患者血清中神经营养指标BDNF(pg/mL)、GDNF(ng/mL)含量的比较如下:干预前,观察组和对照组患者血清中神经营养指标无显著性差异( $P>0.05$ );两组患者干预后4周时血清中BDNF、GDNF的含量均较干预前显著升高( $P<0.05$ ),且观察组患者干预后4周时血清中BDNF、GDNF的含量高于对照组患者( $P<0.05$ )。见表2。

表2 两组干预前后血清中神经营养指标的变化( $n=49, \bar{x} \pm s$ )

组别	时间	BDNF	GDNF
对照组	干预前	4.38±0.57	2.11±0.25
	干预后	7.17±0.85*	3.42±0.38*
观察组	干预前	4.31±0.54	2.09±0.26
	干预后	9.64±1.09* #	4.87±0.57* #

注:组内干预前与干预后比较,\*  $P<0.05$ ;干预后观察组与对照组比较,#  $P<0.05$ 。

## 2.3 氨基酸类神经递质

干预前及干预后4周时,两组患者血清中氨基酸类神经递质Glu(ng/mL)、Asp(ng/mL)、GABA(pg/mL)、Gly(pg/mL)含量的比较如下:干预前,观察组和对照组患者血清中氨基酸类神经递质的含量无显著性差异( $P>0.05$ );两组患者干预后4周时血清中兴奋性氨基酸Glu、Asp的含量较干预前显著降低( $P<0.05$ ),抑制性氨基酸GABA、Gly的含量较干预前显著升高( $P<0.05$ ),且观察组患者干预后4周时血清中兴奋性氨基酸Glu、Asp的含量较对照组患者显著降低( $P<0.05$ ),抑制性氨基酸GABA、Gly的含量较对照组患者显著升高( $P<0.05$ )。见表3。

表3 两组干预前后血清中氨基酸类神经递质含量的变化( $n=49, \bar{x} \pm s$ )

组别	时间	Glu	Asp	GABA	Gly
对照组	干预前	14.39±1.76	20.54±2.74	1.46±0.18	5.35±0.63
	干预后	9.73±1.54*	12.67±1.76*	1.55±0.19*	7.82±0.86*
观察组	干预前	14.51±1.85	21.27±2.86	1.43±0.17	5.49±0.65
	干预后	6.09±0.74* #	7.09±0.87* #	2.17±0.25* #	9.91±1.53* #

注:组内干预前与干预后比较,\*  $P<0.05$ ;干预后观察组与对照组比较,#  $P<0.05$ 。

## 2.4 氧化应激指标

干预前及干预后4周时,血清中氧化应激指标SOD(U/mL)、CAT(U/mL)、MDA(ng/mL)含量的比较如下:干预前,观察组和对照组患者血清中氧化应激指标的含量无显著性差异( $P>0.05$ );两组患者干预后4周时血清中SOD、CAT的含量较干预前显著升高( $P<0.05$ ),MDA的含量较干预前显著降低( $P<0.05$ ),且观察组患者干预后4周时血

清中SOD、CAT的含量较对照组患者显著升高( $P<0.05$ ),MDA的含量较对照组患者显著降低( $P<0.05$ )。见表4。

表4 两组干预前后血清中氧化应激指标含量的变化( $n=49, \bar{x} \pm s$ )

组别	时间	SOD	CAT	MDA
对照组	干预前	45.38±5.61	41.29±5.35	14.38±1.72
	干预后	56.19±6.74*	50.63±5.87*	10.71±1.85*
观察组	干预前	45.27±5.78	40.88±5.27	14.29±1.68
	干预后	78.63±8.45* #	63.41±7.03* #	6.39±0.74* #

注:组内干预前与干预后比较,\*  $P<0.05$ ;干预后观察组与对照组比较,#  $P<0.05$ 。

## 3 讨论

脑外伤患者存在明显的神经损伤,具体表现为智力、语言、吞咽、肢体功能等方面异常,经急诊手术治疗及积极神经营养干预后,仍遗留不同程度功能障碍,严重影响患者的正常生活,严重者甚至导致心境障碍及极端行为。康复训练是神经损伤患者康复期功能锻炼的常用手段,但是多数患者依从性较差无法坚持完成训练内容,或者部分家庭对康复训练的重视程度不足、急诊术后未进行规律训练,目前较多学者推测这是导致脑外伤患者最终治疗结局不佳的重要原因<sup>[5-7]</sup>。康复训练对脑外伤患者的作用既往多停留于主观肢体活动度、肌力等方面,关于血清学层面的研究涉及较少。本次研究在常规神经营养的基础上将规律康复训练引入脑外伤康复期患者,从神经损伤、神经营养、神经递质、氧化应激等方面对其作用进行阐述。

脑外伤患者存在明显的神经功能损伤,较多特异性存在于神经元及神经胶质细胞中的因子从胞内渗透进入胞外,再经损坏的血脑屏障进入外周血,故可在血清中检测到含量上升,且其含量多与患者神经损伤、神经康复程度均密切相关。MBP、NGB、NSE、S-100B均是典型的神经损伤标志物,生理状态下特异性存在于神经细胞中,在循环血中含量甚微,其高表达多预示着神经损伤的存在及临床治疗效果不佳<sup>[8-10]</sup>。本次研究对比两组患者干预前后血清中上述神经损伤指标含量的差异,发现:与干预前比较,两组患者干预后血清中神经损伤指标MBP、NGB、NSE、S-100B的含量均较低;进一步与对照组比较,观察组患者血清中MBP、NGB、NSE、S-100B的含量较低,证实了在神经营养治疗基础上加入规律康复训练,可有效降低患者的神经损伤程度,这也是患者肢体功能得到宏观恢复的内在原因。

神经营养/神经损伤是一对相互制衡的因素,已经明确联合治疗可减轻神经损伤,本次研究进一步对比两组患者神经营养标志物含量的差异。BDNF

是具有神经营养作用的蛋白质,生理状态下在人体神经系统广泛表达,通过增加抗凋亡蛋白基因表达来促进神经细胞生存。GDNF 来源于神经胶质细胞,其高表达有助于神经胶质细胞的营养及存活<sup>[11,12]</sup>。本次研究发现:与干预前比较,两组患者干预后血清中 BDNF、GDNF 的含量较高;进一步与对照组比较,观察组患者干预后血清中 BDNF、GDNF 的含量较高,证实康复训练联合神经营养治疗可增加神经营养因子的含量,进一步促使神经营养/神经损伤平衡向神经细胞康复方向漂移。多种神经递质参与了神经损伤、神经修复过程,其中神经损伤发生后早期兴奋性氨基酸 Glu、Asp 的表达量即刻大幅增加,具有强烈的神经毒性,可进一步加剧神经损伤发生<sup>[13,14]</sup>;GABA、Gly 属于抑制性氨基酸,生理状态下与兴奋性氨基酸的表达量处于动态平衡,其表达减少可减轻对兴奋性氨基酸的抑制作用及对神经元的保护作用<sup>[15,16]</sup>。本次研究对比两组患者血清兴奋性/抑制性氨基酸表达量的差异,发现:与干预前比较,两组患者血清中兴奋性氨基酸 Glu、Asp 的含量较低,抑制性氨基酸 GABA、Gly 的含量较高;进一步与对照组比较,观察组患者干预后血清中兴奋性氨基酸 Glu、Asp 的含量较低,抑制性氨基酸 GABA、Gly 的含量较高,证实康复训练联合神经营养治疗可有效均衡氨基酸类神经递质的表达,减少神经损伤。

脑损伤及手术后缺血再灌注损伤过程,均有氧化应激反应的参与,换言之患者脑局部及全身氧化应激反应程度与病情严重程度、治疗预后均密切相关<sup>[17]</sup>。SOD、CAT 是具有抗氧化作用的因子,可中和过量产生的氧自由基及脂质氧化产物,避免组织脏器损伤;MDA 是典型的氧化代谢产物,其含量与机体氧化损伤程度一致<sup>[18]</sup>。本次研究对比两组患者干预前后血清中上述氧化应激指标含量的差异,发现:与干预前比较,两组患者干预后血清中 SOD、CAT 的含量较高,MDA 的含量较低;进一步与对照组比较,观察组患者干预后血清中 SOD、CAT 的含量较高,MDA 的含量较低,证实康复训练联合神经营养治疗可有效降低机体氧化应激反应,这也是其减少神经损伤、促进躯体功能恢复的重要机制之一。

脑外伤康复期患者接受康复训练联合神经营养治疗,可有效减少神经损伤、增强神经保护作用,减轻全身氧化应激反应,较单纯神经营养治疗而言,是更为高效合理的康复期治疗方式,值得在日后临床实践中推广应用。

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情绪的神经递质,通过作用于突触后膜的 5-HT<sub>1A</sub> 受体和 5-HT<sub>2</sub> 受体来调节情绪<sup>[15,16]</sup>。在卒中后焦虑的发生过程中 NE、DA、5-HT 等单胺类神经递质的分泌明显减少。我们通过分析治疗前后血清中单胺类神经递质含量的变化可知:两组患者治疗后血清中 NE、DA、5-HT 的含量均高于治疗前且针灸组患者治疗后血清中 NE、DA、5-HT $\alpha$  的含量均高于对照组。这就说明常规治疗手段能够在一定程度上减少卒中后抑郁患者康复过程中单胺类神经递质的分泌,联合使用针灸辅助治疗能够更进一步抑制单胺类神经递质的分泌并改善抑郁情绪。

针灸辅助治疗用于卒中后抑郁能够有效改善抑郁情绪,增加神经细胞因子分泌、减少炎症细胞因子分泌并调节单胺类神经递质的功能是针灸改善抑郁情绪的分子途径。

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