·综述·

电针对脊髓损伤后干细胞移植疗效的影响

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脊髓损伤(spinal cord injury,SCI)是中枢神经系统的一种严重外伤性疾患,能导致脊髓损伤平面以下感觉、运动、反射及植物神经功能等障碍,该病年发生率为(12.1~57.8)/100 万,因其致死率、致残率较高,给患者家庭及社会带来沉重负担。SCI 后修复一直是神经康复领域的难点及热点,国内、外治疗 SCI 常用的传统方法包括手术、药物、康复训练等,虽然能在一定程度上缓解临床症状,但 SCI 后功能残疾依然难以避免,并且上述疗法并不能从根本上解决神经元再生问题[1]。干细胞(stem cells)具有多向分化潜能,可诱导分化为神经细胞,促进 SCI 后神经组织修复及再生[2];电针(electric acupuncture,EA)用于治疗 SCI 的临床疗效肯定,能减轻继发性损伤、缓解疼痛[3]。相关动物实验发现,EA 联合干细胞移植能促进干细胞存活、分化与迁移,加速 SCI 大鼠神经轴突再生,进而显著改善大鼠受损神经功能,但其确切作用机制仍未完全明确。本文现就 EA 对干细胞移植后 SCI 损伤局部微环境的改善以及对神经轴突再生和干细胞迁移、增殖、分化的促进作用进行总结,并归纳近年来关于 EA 干预对 SCI 后干细胞移植的可能调控机制。

干细胞移植治疗 SCI

干细胞是一类具有自我复制能力的多潜能细胞,它存在于所有多细胞组织体内,能通过有丝分裂与分化形成多种特定细胞,同时还可通过自我更新以提供更多干细胞。哺乳动物的干细胞可分为胚胎干细胞与成体干细胞,胚胎干细胞主要来自囊胚里的内细胞团,而成体干细胞则来自各式各样机体组织。SCI 后最终神经学损伤主要由原发性损伤和继发性损伤共同引起,目前治疗策略则更多集中于防治局部继发性损伤、促进神经轴突再生以及替换受损神经细胞等方面。干细胞移植是治疗 SCI 行之有效的治疗手段之一[4],通过移植干细胞能够修复受损内环境,并为神经通路重塑提供结构支持,加速神经髓鞘形成,增加局部微环境中神经营养因子含量,发挥神经营养及内生性激活作用[5];SCI 后移植的神经干细胞能向损伤处迁移、存活并增殖,分化为神经元或星形胶质细胞、少突胶质细胞等成熟细胞,实现神经细胞轴突与髓鞘再生,从而建立功能性神经突触连接,并促使残存脱髓鞘神经纤维和新生神经纤维形成新的髓鞘,保持神经纤维功能完整性,加速受损神经功能恢复[4]。

目前干细胞移植存在的主要技术难题包括神经元存活率、迁移率及分化率低,此外干细胞内一些营养因子作用尚不清楚,且其营养效应不能长期保存[6]。目前关于干细胞的神经保护、促神经轴索生长以及修复研究尚处于实验阶段,在实际临床应用中还存在诸多局限[2]。上述问题在今后基础及临床研究中均有待进一步探索。

EA 干预对 SCI 后干细胞移植的影响

目前临床已广泛采用 EA 治疗 SCI 后功能障碍并取得显著疗效。EA 是利用电针治疗仪输出脉冲电流,通过毫针作用于人体经络腧穴或体表局部,从而达到疾病治疗目的。EA 疗法将毫针针刺与电刺激相结合,具有针刺与电刺激双重疗效[7]。以往关于 EA 治疗 SCI 的作用机制大致可归纳为减轻继发性损伤、促进神经轴突再生、加速神经干细胞增殖等[8-9]。

早期 EA 治疗能减轻和延缓 SCI 后病理损伤,减轻疾病初期继发性损伤,促进脊髓受损神经功能修复[10]。同时有研究发现,EA 干预可诱导移植干细胞分化更多神经元,促进受损脊髓组织轴突再生、突触连接并形成神经网络;同时还能激活细胞新陈代谢,并启动、分泌内源性神经因子,促进上、下行神经纤维再生,从而修复受损脊髓结构与功能[3,8],但其具体作用机制尚未明确。

一、EA 干预对干细胞移植微环境的调节

有学者研究发现,神经生长因子及相关凋亡基因与神经系统发育、信号通路、神经元存活密切相关[11],EA 能通过调节细胞因子、神经营养因子(neurotrophic factors,NTFs)、细胞凋亡基因、Nogo 蛋白、钙离子等表达水平来促进受损组织修复[12]。Yamasaki 等[13]研究 EA 干预对 SCI 大鼠脊髓前角运动神经元功能的影响,采用 RT-PCR 技术检测脊髓受损区神经胶质细胞源性的神经营养因子(glial cell line-derived neurotrophic factor,GDNF)mRNA 表达变化,并通过尼氏染色、酶组织化学染色法观察大鼠 SCI 后受损脊髓前角运动神经元存活数量及乙酰胆碱酯酶(acetylcholine esterase,AChE)变化情况,同时采用斜板试验和 BBB(Basso,Beattie and Bresnahan)评分法观察大鼠后肢运动功能恢复情况,发现 SCI 后进行干细胞移植并辅以 EA 干预,可促进 GDNF mRNA 表达上调,脊髓前角运动神经元存活数量增加,同时还能增强乙酰胆碱酯酶活性,提示 EA 对 SCI 大鼠前角运动神经元功能恢复具有显著促进作用。Liu 等[7]在探讨督脉电针(governor vessel electro-acupuncture,GV-EA)联合干细胞移植对受损脊髓修复作用时也指出,GV-EA 干预可刺激 SCI 局部组织细胞新陈代谢及内环境合成、分泌内源性神经营养因子,进而促进 SCI 后神经结构及功能修复。

二、EA 干预促进神经轴突再生

脑源性神经营养因子(brain derived neurotrophic factor,BDNF)可通过抵抗损伤刺激,保护缺血、缺氧神经元,诱导轴突再生并促进神经通路形成,而 EA 干预能促进 BDNF 在受损脊髓中表达[14]。Semaphorins 家族是一类信号蛋白,共包括 20 多个重要成员,Semaphorins 分子不但能通过调节神经生长锥束导

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向轴突生长方向,还参与细胞迁移、肿瘤生长和免疫反应等多种生理功能,该家族中的人臂板蛋白 3A(Sema3A)在神经发育时能直接诱导少突胶质细胞祖细胞迁移,对 SCI 修复具有重要调控作用[15]。Ding 等[16]研究发现,EA 干预对 SCI 后神经生长抑制因子 Sema3A 表达具有影响作用,采用免疫组织化学法(ABC 法)和图像分析技术检测受损脊髓内 Sema3A 表达,发现早期 EA 干预能促进 SCI 后 Sema3A 表达,从而增强 Sema3A 对迷乱性出芽的抑制作用,有利于轴突正确出芽。大鼠 SCI 后伴有 DNA 结合抑制物 2(inhibitor of DNA binding 2,Id2)表达上调,该细胞因子能负向调控髓鞘碱性蛋白(myelin basic protein,MBP)基因启动子活性,使 MBP 表达下降,这也是 SCI 后神经纤维脱髓鞘病变的重要机制之一。Ariza 等[17]通过研究 EA 对大鼠脊髓压迫性损伤后髓鞘再生的影响,采用电镜观察 SCI 节段髓鞘超微结构,并采用免疫印迹技术和免疫荧光双标法从分子水平检测 Id2 及 MBP 表达变化,发现 EA 干预能下调 Id2 表达,从而正向调控 MBP 以增强其表达,促进少突胶质细胞增殖,帮助神经纤维再髓鞘化,有利于受损脊髓神经功能改善。

三、EA 干预促进移植干细胞迁移、增殖及分化

有研究采用 EA 及骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMSCs)移植联合治疗 SCI 大鼠,发现 EA 干预能显著促进 BMSCs 存活、分化及迁移,对 SCI 大鼠神经功能恢复具有明显促进作用[18]。SCI 后中枢神经系统神经营养因子 3(neurotrophins-3,NT-3)呈一过性表达,EA 干预可能通过增强 NT-3 表达,从而促使 NT-3 结合并激活酪氨酸激酶受体 B(tyrosine kinase receptor B,TrkB)和酪氨酸激酶受体 C(tyrosine kinase receptor C,TrkC),通过细胞信号转导途径对细胞存活及轴突髓鞘形成发挥积极作用[19]。Yan 等[20]通过建立对照组、EA 治疗组、间充质干细胞(mesenchymal stem cells,MSCs)移植组和 EA + MSCs 移植组,观察 EA 干预对 SCI 后移植 MSCs 分化、神经纤维再生以及局部神经功能恢复的影响,发现 EA 干预能促进 MSCs 分化,同时还能诱导内源性 NT-3 表达,促进神经纤维再生。另有研究报道,EA 干预还可通过促使大鼠脊髓表达神经生长因子及其受体-酪氨酸激酶受体 A(tyrosine kinase receptor A,TrkA)来加速受损神经元修复,从而改善大鼠受损神经功能[21]。Ding 等[22]发现 EA 干预可促进 MSCs 移植后 NT-3 表达,提高 TrkC 含量,促进少突样细胞从 NT-3 受体基因介导的 MSCs 中分化,改善脱髓鞘 SCI 大鼠受损髓鞘及加速神经功能修复,从而保护受损脊髓组织。此外在受损神经轴突附近辅以 EA 刺激可促进神经轴突再生,并调节机体自由基、脊髓神经递质、水、电解质、神经营养因子及脊髓 B-细胞淋巴瘤/白血病-2(B cell lymphoma/leukmia-2,Bcl-2)基因和蛋白表达,改善神经生长微环境[17]。

当发生 SCI 后,受损脊髓局部会产生内源性损伤电流,这种电流能使神经元胞浆内 Na^+、Ca^{2+} 离子增多,后者能破坏神经丝,促使轴突变性[23]。EA 干预能阻止受损脊髓局部产生内源性损伤电流,从而抑制过量 Ca^{2+} 内流入神经元而发挥治疗作用[24]。EA 治疗过程中,其电场效应可使轴索膜内带电蛋白质受体发生移动,促使多种神经趋化因子向电场负极方向聚集,诱导神经元向直流电场阴极方向显著生长,从而促进神经元轴突生长及神经功能恢复。而早在 1986 年 Borgens 等学者[24]已应用置入式直流电电场治疗脊髓背侧横断豚鼠,发现具有一定疗效。1988 年 Fehling[25]应用直流电电场治疗 SCI 大鼠,发现能促进哺乳类动物脊髓轴突再生。另外还有研究报道,由于 EA 干预能改变神经元电活动,这可能也是 EA 干预促进少突胶质前体细胞(oligodendrocyte progenitor cells,OPCs)增殖及分化的重要原因[26]。

EA 治疗主要参数选择

在与干细胞移植联合治疗 SCI 时,EA 选穴及刺激频率、波型、强度等均是需要重点考虑的治疗参数。EA 作用穴位对其疗效具有重要影响,临床针对 SCI 患者以针刺督脉穴位最为常见,夹脊穴次之。从祖国中医理论分析,督脉循行于后背正中,贯穿整个脊柱,行于脊里,上行入脑,并从脊里分出属肾,与脑、脊髓和肾脏功能具有密切联系。由 SCI 导致的外伤性截瘫,从中医角度分析是督脉受损,采用 EA 刺激督脉经穴及夹脊穴治疗 SCI,既可直达病所、疏通督脉使阳气通达,又可调理气血、行气活血生髓[27]。现代细胞生物学研究表明,早期 GV-EA 治疗可促进受损脊髓细胞合成及分泌内源性 NT-3,从而提高受损脊髓 BMSCs 分化程度,加速神经纤维重建[28],这可能是 EA 干预提高干细胞移植治疗 SCI 疗效的重要原因之一。叶飞等[29]研究 EA 刺激大鼠双侧足三里穴对脑梗死大鼠内源性神经干细胞及神经功能恢复的影响,将造模后脑梗死大鼠分为对照组及 EA 组,各组又按照 6 个不同时间点细分为 6 个亚组,采用横木实验(beam walking test,BWT)评定各组大鼠肢体功能恢复情况,同时采用 5-溴脱氧尿嘧啶核苷(5-Bromo-2-deoxyUridine,BrdU)标记增殖神经细胞,应用半定量法分析碱性成纤维生长因子(basic fibroblast growth factor,bFGF)mRNA 表达情况,发现 EA 干预能促进神经干细胞增殖、分化,同时还有助于脑梗死大鼠偏瘫侧肢体功能恢复,可见 EA 刺激特定穴位(如足三里穴等)对干细胞移植疗效确有促进作用。降钙素基因相关肽(calcitonin gene related peptide,CGRP)是在机体中枢及外周神经系统中发现的一种新型神经肽,在神经系统疾病发生过程中具有着重要作用,在 SCI 早期其表达水平可作为评价脊髓修复再生的一项重要指标;阮经文等[30]分别采取艾灸与 EA 刺激督脉腧穴,并观察对 SCI 大鼠受损脊髓 CGRP 表达的影响,发现 GV-EA 治疗可显著促进 SCI 大鼠受损脊髓组织 CGRP 表达,对 SCI 后神经功能康复具有显著促进作用。以上穴位均是 EA 治疗 SCI 时常用穴位,均对干细胞移植治疗 SCI 疗效具有促进作用。

目前国内、外关于 EA 或电刺激治疗 SCI 后功能障碍的研究均以动物实验居多,临床观察偏少;在 EA 刺激频率方面,动物实验多选用 1 ~ 3 Hz,临床治疗时选用频率通常高于 1 ~ 3 Hz,但目前尚无统一规范标准;常用刺激波型包括疏密波、断续波和连续波等,其中以疏密波及连续波使用较多;在刺激强度方面,实验动物以局部或全身肌肉出现轻微抽动或摆尾动作为宜,临床治疗时多以患者能耐受为度[31-33]。

结语

SCI 是临床常见的严重神经损伤性疾病。干细胞疗法是促进 SCI 后功能修复的新兴技术,能抑制神经细胞凋亡、补充缺失的神经组织、改善神经组织再生微环境、减少瘢痕形成等,可明显改善 SCI 患者受损神经功能及生活质量;EA 干预能减轻 SCI

后局部继发性损伤、促进轴突再生及神经干细胞增殖。在干细胞移植基础上辅以 EA 干预,可促进移植神经干细胞在 SCI 局部分化为神经元,同时还能激活细胞代谢过程、启动和分泌内源性神经因子,进而促进神经通路恢复,加速受损脊髓结构及功能修复,其可能作用机制包括:通过调控细胞因子、NTFs、细胞凋亡基因等表达,从而提供适于功能修复的微环境;通过保护缺血、缺氧神经元,诱导并促进神经通路形成,促进少突胶质细胞增殖,加速神经纤维再髓鞘化及神经轴突再生;通过促进细胞存活、轴突髓鞘形成、改变神经元电活动等,有助于移植干细胞迁移、增殖及分化。目前临床上主要选取督脉穴及夹脊穴作为电针刺激部位,其电刺激频率、波型、强度等参数选择常因治疗对象不同而相应调整,关于 EA 的治疗参数选择至今尚无统一标准。目前 EA 联合干细胞移植治疗 SCI 主要以基础动物实验居多,临床尚未广泛开展应用,但该疗法具有良好的应用前景,值得进一步深入探讨。

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Anti-seizure medications and intelligence quotient

BACKGROUND AND OBJECTIVE Some antiepileptic drugs (AEDs) have been shown to interfere with normal brain development early in life. In addition it is well recognized that many AEDs can adversely affect cognition. This study investigated the effect of drug withdrawal on intelligence after epilepsy surgery.

METHODS The Time to Stop (TTS) study, a retrospective, European, multicentre, cohort study, collected data regarding AED withdrawal as related to seizure outcome. Subjects were patients younger than 18 years of age at the time of surgery, who began AED reduction postoperatively, all with at least one year of postoperative follow-up. All participants had undergone pre-and at least one post-operative neuropsychological assessment. Analyzed were the association between AED withdrawal, IQ and delta IQ.

RESULTS The mean age at surgery was 9.6 years, with a mean of 19.8 months between surgery and the latest neuropsychological assessment. The mean IQ change for all patients who reduced or stopped AEDs was 4.6 points, while that for those who achieved complete withdrawal was 5.6. A significant relationship was found between the number of AEDs reduced and a greater gain in IQ ($P<0.001$).

CONCLUSION This study of children undergoing epilepsy surgery found that withdrawal of antiepileptic drugs is independently associated with improvement in intelligence quotient.

【摘自:Boshuisen K, van Schooneveld MM, Uiterwaal CS, et al. Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. Ann Neurol, 2015,78(1): 101-114.】

Cholinesterase inhibitors for parkinson's disease

BACKGROUND AND OBJECTIVE Among the non-motor features of Parkinson's disease (PD), cognitive impairment has been shown to have a high, negative impact on the patient's quality of life. Postmortem studies of patients with PD have shown degeneration of cholinergic and nigrostriatal pathways. This systematic review was undertaken to clarify the efficacy of cholinesterase inhibitors (ChIs) for symptoms of PD.

METHODS Four databases were searched with 945 articles identified by the initial search. From these, four randomized, controlled trials, were included in the meta-analysis. Among those were one comparing rivastagmine with placebo, and three comparing donepezil with placebo. The primary outcome measure was cognitive function, assessed using the Mini Mental State Examination, and rate of falls. Safety measures and secondary outcomes were also included.

RESULTS The meta-analysis revealed that ChIs significantly slowed MMSE decline ($P=0.001$), without improving the risk of falls ($P=0.681$). Alzheimer's Disease Assessment-cognitive subscale, global assessment and behavioral disturbance improved in the ChIs group ($P<0.001$, $P<0.001$ and $P=0.025$, respectively), without impacting disability ($P=0.053$). Death rate was significantly decreased in the ChIs group (odds ratio 0.295; $P=0.01$). Increased tremor rates and adverse reactions were noted in the ChIs group ($P=0.001$ and $P<0.0001$, respectively).

CONCLUSION This meta-analysis of patients with Parkinson's disease, treated with cholinesterase inhibitors, found that these medications can treat cognitive impairment but do not significantly improve gait dysfunction and fall risk.

【摘自:Pagano G, Rengo G, Pasqualetti G, et al. Cholinesterase inhibitors for parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiat, 2015, 86(7): 767-773.】