

周围神经病脊髓电刺激术治疗进展

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【摘要】 脊髓电刺激术是一种微侵袭神经调控技术,在糖尿病周围神经病变、三叉神经痛和三叉神经带状疱疹后神经痛、化疗诱导的周围神经病变、慢性腹股沟疼痛、腰骶神经根综合征等周围神经病中广泛应用且疗效得到认可。本文对脊髓电刺激术基本原理及其在周围神经病中的应用进展展开综述,以促进脊髓电刺激术在周围神经病中的临床应用。

【关键词】 周围神经系统疾病; 脊髓; 电刺激疗法; 综述

Progress on spinal cord stimulation in treatment of peripheral neuropathy

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【Abstract】 Spinal cord stimulation (SCS) is a minimally invasive neuromodulation technique that has been widely applied and recognized for its efficacy in peripheral neuropathy such as diabetic peripheral neuropathy (DPN), trigeminal neuralgia (TN), trigeminal postherpetic neuralgia, chemotherapy-induced peripheral neuropathy (CIPN), chronic groin pain, and lumbosacral radiculopathy syndrome. This article reviews the basic principles of SCS and its latest applications in peripheral neuropathy to promote its clinical application in peripheral neuropathy.

【Key words】 Peripheral nervous system diseases; Spinal cord; Electric stimulation therapy; Review

Conflicts of interest: none declared

周围神经病是临床常见的神经系统疾病,可导致周围神经系统神经元炎症或坏死、轴突变性和细胞结构畸变^[1]。其病因多为创伤、中毒、代谢、免疫和遗传等,具有较高的病残率和较重的经济负担,严重降低患者生活质量^[2]。目前虽有多种周围神经损伤修复方法,但存在诸多局限,如自体神经移植虽是标准治疗方法,但受限于供体部位和可用组织常难以实施、移植后不能完全恢复、多次手术和神经瘤形成^[3-4]。因此,需要探寻新的生物材料和细胞治疗方法,以改善神经损伤后的修复效果^[5]。脊髓电刺激术(SCS)作为一种新兴的神经调控技术,已广泛应用于周围神经病的治疗^[6-8]。本文拟就脊髓电刺激术原理及技术进展、周围神经病病理学类型和组织学特点,以及脊髓电刺激术在糖尿病周围神经病变(DPN)、三叉神经痛(TN)、化疗诱导的周围

神经病变(CIPN)及其他周围神经病治疗中的最新进展进行综述,以为脊髓电刺激术的临床推广提供依据。

一、脊髓电刺激术简介

脊髓电刺激术是通过微侵袭手术方式将刺激电极植入脊髓节段的硬脊膜外隙,并通过一定频率的电脉冲刺激相应脊髓背角神经元及传导束,以实现神经调控的一种新兴神经调控微侵袭技术^[9]。脊髓电刺激术在多种病因诱发的神经病理性疼痛的治疗中具有较好疗效和安全性^[10],其在缓解脊髓损伤所致神经病理性疼痛方面疗效显著,可一定程度恢复受损脊髓的正常生理功能^[11]。脊髓电刺激术还可用于外伤性脊髓损伤后的脊髓及周围神经系统功能恢复和肢体运动功能恢复,通过多种机制增强神经可塑性,改善运动功能和自主神经功能^[12]。

脊髓电刺激术直接作用于相应脊髓节段可促进受损的脊髓神经细胞再生,促进脊髓损伤修复。通过改变电刺激频率以恢复神经元的可塑性,激活脊髓神经回路,促进损伤后神经再生和轴突连续性

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的恢复,帮助患者恢复基本运动功能^[13]。通过硬脊膜外植入的片状电极,将神经刺激器产生的电流传至脊髓,改变疼痛信号的传递,阻断疼痛感上传至疼痛中枢,达到缓解疼痛的目的^[14]。神经病理性疼痛患者在接受脊髓电刺激术后,视觉模拟评分(VAS)评分显著降低且生活质量得以改善^[15-18]。脊髓电刺激术的另一重要应用是促进受损神经再生,激活脊髓源性神经干细胞(SC-NSCs),从而促进神经元的增殖和分化^[19]。这一过程可能与经典Wnt信号转导通路的激活有关,为神经损伤后修复提供新的治疗思路^[20]。

脊髓电刺激术作为一种神经调控技术,正在改变中枢和周围神经损伤患者的治疗与康复方式。通过改变电刺激频率等方式刺激脊髓并结合相应的康复训练,患者可以在运动功能恢复和受损神经再生方面显著获益^[21-22]。

二、周围神经病基本病理学类型及组织学特点

周围神经病具有多种病理学特征及其相对应的组织学特点,致病因素包括外伤、神经卡压、代谢、中毒、感染和炎症等^[23]。周围神经病所致神经损伤可分为4种基本病理学类型,即轴突损伤、沃勒变性、髓鞘损伤和神经元变性^[24-25]。周围神经组织学特征随之发生显著改变,因此,确定病变病理学类型对受损神经修复和再生至关重要^[26]。(1)轴突损伤:在轴突损伤过程中,由于中毒性或代谢性疾病阻碍神经元蛋白合成,影响神经纤维的完整性,导致信号传递中断,无法滋养轴索远端,出现由远至近的轴索变性;同时轴突损伤通常伴有神经炎症反应,而浸润的炎性细胞进一步加重神经损伤^[27]。(2)沃勒变性:常见于神经纤维因外伤离断,离断处远端和近端发生神经纤维轴索变性、髓鞘脱失,随后产生的细胞碎片由巨噬细胞吞噬^[28]。(3)髓鞘损伤:主要为周围神经施万细胞的免疫性损伤,如吉兰-巴雷综合征(GBS)主要影响髓鞘的形成和维持,其病理学特点为髓鞘板层分离、肿胀、断裂和脱失,进而影响神经传导,而轴索相对保留^[29]。髓鞘损伤多病程较长或慢性反复发作,故髓鞘病变程度与神经再生密切相关^[30]。(4)神经元变性:神经元变性导致神经纤维再生能力下降,神经元代谢紊乱,继发神经元的整体崩解坏死,无再生迹象,尤其是在老年周围神经病患者群体中,可见神经元再生能力显著降低^[31]。此现象可能与神经元凋亡和神经元炎症反应的增强有关,进而导致神经延迟修复或不修

复^[32]。上述研究提示,周围神经损伤后病理学类型及其组织学特点对理解神经损伤机制和选择治疗方式具有重要意义。

三、脊髓电刺激术在周围神经病中的应用

1. 糖尿病周围神经病变 糖尿病周围神经病变是糖尿病患者最常见的长期并发症,主要包括远端对称性多发性神经病(DSPN)和糖尿病自主神经病变^[33]。>50%的糖尿病可进展为糖尿病远端对称性多发性神经病变^[34],其中约1/3进展为痛性糖尿病神经病变(PDN),但药物治疗有嗜睡、头晕、头痛、食欲减退等不良反应,且部分药物可导致成瘾性^[35],亟待寻求如脊髓电刺激术等新型治疗方法。有研究共纳入216例难治性痛性糖尿病神经病变患者,初期纳入时随机接受脊髓电刺激术(10 kHz)+常规医疗管理(113例)、单纯常规医疗管理(103例),在24个月的随访期内,最终有142例患者接受脊髓电刺激术,其健康相关生活质量(HRQoL)和睡眠质量均显著改善,90.14%(128/142)的患者疼痛缓解率至少为50%,65.49%(93/142)的患者表现出具有临床意义的神经功能恢复^[36]。与药物治疗相比,低频(<500 Hz)和超高频(>10 kHz)脊髓电刺激术均可改善痛性糖尿病神经病变患者的疼痛症状,随访至术后6个月时,95例药物治疗患者中仅1例(1.05%)达到疼痛缓解,88例接受超高频脊髓电刺激术的患者中53例(60.23%)达到疼痛缓解($P < 0.001$)。研究表明,不同频率的电刺激也可能影响治疗效果,与低频刺激相比,超高频脊髓电刺激术治疗痛性糖尿病神经病变的疗效更显著^[37-38]。一项针对周围神经病患者的临床研究纳入9例痛性糖尿病神经病变患者,对其中8例成功进行超高频脊髓电刺激术(频率10 kHz,脉宽30 μ s),结果发现,7例患者疼痛缓解率 $\geq 50%$;8例相关疼痛症状得以缓解,疼痛对睡眠的干扰不断减少,整体功能提高,且术后6和12个月随访时症状持续改善^[38]。若生活方式管理和药物控制血糖未能奏效,可采用超高频脊髓电刺激术对痛性糖尿病神经病变进行神经调控治疗^[39]。与低频刺激相比,超高频脊髓电刺激术患者随访18个月时疼痛平均减轻73%($P < 0.001$)^[40]。此外,脊髓电刺激术还可减少患者对镇痛药物的依赖,部分患者下肢感觉障碍也有所改善^[41-42]。脊髓电刺激术对糖尿病性下肢疼痛有更明显的治疗效果,多项随机对照临床试验证据支持脊髓电刺激术可明显缓解痛性糖尿病神经病变患者的下肢疼痛^[43-44]。脊髓电

刺激术不仅可以缓解痛性糖尿病足疼痛,促进溃疡面愈合,还可以改善患肢血流动力学,促进患肢神经功能恢复^[16,45-46]。尽管脊髓电刺激术在治疗糖尿病周围神经病变方面显示出良好的应用前景,但尚待开展更多高质量研究进一步验证其长期疗效和安全性^[45,47]。

2. 三叉神经痛和三叉神经带状疱疹后神经痛 三叉神经痛是第 V 对脑神经(三叉神经)1 个或多个分支的慢性神经性疼痛。通常为骤发骤停的单体三叉神经支配区电击样疼痛,疼痛呈周期性发作。可分为两大类,一是与神经炎症和畸形血管压迫等原因有关的原发性三叉神经痛;二是诱因不明且常呈持续性疼痛的特发性三叉神经痛^[48-49]。虽然三叉神经痛的具体病理生理学机制尚待阐明,但其疼痛的门控效应^[50]使脊髓电刺激术仍可作为药物治疗和手术切除神经失败后的首选治疗方法。Velásquez 等^[51]对采用高颈位脊髓电刺激术(ucSCS)治疗的 12 例三叉神经痛患者进行回顾分析发现,在平均 4.4 年的随访期中,3 例长期疼痛未能减轻,余 9 例平均疼痛缓解率为 57.10%。Edelbach 和 Lopez-Gonzalez^[52]采用高颈位脊髓电刺激术治疗 1 例女性难治性三叉神经痛患者,结果发现,刺激期间(频率 300 Hz,脉宽 170 ms,强度 0.50~0.80 mA),疼痛缓解率为 60%;经过 4 周的短期随访,患者自述第 1 次刺激后生活质量显著改善,饮食及日常活动有所改善,VAS 评分为 6 分。三叉神经带状疱疹后神经痛(TG-PHN)是最常见和最复杂的带状疱疹后神经痛(PHN)之一。其具有独特的临床和病理生理学特征,是由水痘-带状疱疹病毒(VZV)感染三叉神经节而引起,随病情迁延可损伤头部上行和下行神经调节通路^[53]。有研究采用短时程高颈位脊髓电刺激术联合周围神经电刺激术(PNS)成功治疗 1 例 V2 支和 V3 支三叉神经带状疱疹后神经痛的 83 岁女性患者,高颈位脊髓电刺激术刺激参数为脉宽 400 μ s、频率 60 Hz、强度 5 mA、接触极性 2+和 6-;周围神经电刺激术刺激参数脉宽 20 ms、频率 2 Hz、持续 900 s、电压 40~80 V,结果发现疼痛明显缓解^[54]。高颈位脊髓电刺激术通过硬脊膜外隙的刺激电极,释放电流刺激脊髓背侧,激活抑制性中间神经元并减弱上行疼痛传递,提示 C₁₋₂ 节段的短时程高颈位脊髓电刺激术是治疗老年三叉神经带状疱疹后神经痛的有效手段。此外,脊髓电刺激术联合三叉神经半月神经节刺激术(TSGS)等神经调控技术也可

用于治疗三叉神经带状疱疹后神经痛^[55]。不同神经调控技术的联合为该病的治疗提供了更多元化方案。

3. 化疗诱导的周围神经病变 化疗诱导的周围神经病变是多种一线化疗药物最常见的痛性并伴随乏力的药物不良反应^[56]。病因多为化疗药物引发神经毒性导致对称性感觉、运动障碍和神经功能障碍,表现为烧灼样刺痛或麻木,通常呈“手套和袜套”样感觉减退,可伴肢体无力、步态异常和其他自主神经功能障碍^[57]。虽然急性化疗诱发的周围神经病变可能随化疗的完成而消退,但相当一部分患者停药后仍受其持续困扰,且常用的药物治疗和介入治疗多模式管理难以抑制病情恶化^[57-59]。脊髓电刺激术逐渐成为难治性化疗诱导的周围神经病变的首选神经调控技术,疼痛缓解率 > 50%^[60];且步态评分、VAS 评分和定量感觉检测(QST)评分均显著改善^[61]。提示脊髓电刺激术可明显缓解化疗诱导的周围神经病变相关疼痛,并对步态障碍产生积极影响;此外,QST 检测所示振动与触摸阈值、本体感觉、感觉温度等结果的改善亦提示脊髓电刺激术在周围神经修复中的潜在价值^[61]。

4. 其他周围神经病 (1)慢性腹股沟疼痛:目前,神经松解术、腹股沟管管壁修复和粘连清创术等一般手术治疗虽可以短期内缓解慢性腹股沟疼痛^[62],但长期疗效仍不理想^[63-64]。一项回顾性研究纳入 29 例接受脊髓电刺激术治疗的慢性腹股沟疼痛患者,随访 27.8 周发现,82.61%(19/23)的患者疼痛缓解率 > 50%^[65]。此外,缝合后疼痛、难治性睾丸疼痛、背部手术失败后综合征等多种难治性疼痛予脊髓电刺激术后疼痛均显著缓解^[65],提示脊髓电刺激术治疗局部特定疼痛效果良好。(2)腰骶神经根综合征(LRS):腰骶神经根综合征亦称坐骨神经痛、梨状肌综合征或神经根疼痛^[66],其特点是沿 1 个或多个腰骶神经节段放射的疼痛,伴或不伴其他神经根症状,如感觉或运动功能减退。超高频(10 kHz)刺激对腰骶神经根综合征疼痛缓解有效,已在欧洲获准进入临床应用^[67]。一项针对未曾接受脊椎手术的难治性慢性腰骶神经根综合征患者进行脊髓电刺激术的系统性回顾研究发现,术后 12 个月随访时,与对照组(鞘内给药)相比,脊髓电刺激术组数字评价量表(NRS)疼痛评分减少(62%对 0, $P < 0.001$),且在提物、步行、站立、睡眠等生活自理能力方面均有所改善^[68-69]。对于无法接受手术治疗、药

物治疗效果差和神经减压术失败的难治性慢性腰骶神经根综合征患者,脊髓电刺激术可明显缓解难治性疼痛,提高生活质量^[70]。

综上所述,脊髓电刺激术治疗糖尿病周围神经病变、三叉神经痛和化疗诱导的周围神经病变等周围神经病具有较好疗效;且为微侵袭技术,具有较高的安全性。目前对脊髓电刺激术的作用机制研究正不断深入,对刺激靶点更精准的定位以及新型材料的应用可使长期调控作用更加稳定,对患者的损伤更轻微。相信随着神经调控技术的发展,脊髓电刺激术有可能成为神经调控治疗周围神经病的新方向。

利益冲突 无

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· 小词典 ·

中英文对照名词词汇(六)

- 硬膜外运动皮质电刺激
epidural motor cortex stimulation (eMCS)
- 硬膜下运动皮质电刺激
subdural motor cortex stimulation (sMCS)
- 诱发的复合动作电位
evoked compound action potentials (ECAP)
- Glasgow 预后分级 Glasgow Outcome Scale (GOS)
- 远端对称性多发性神经病
distal symmetrical polyneuropathy (DSPN)
- 运动皮质电刺激术 motor cortex electrical stimulation (MCS)
- 运动想象 motor imagery (MI)
- 振动触觉刺激 vibro-tactile stimulation (VTS)
- Holmes 震颤 Holmes tremor (HT)
- Fahn-Tolosa-Marin 震颤评价量表
Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS)
- 正中核-腹内核
centromedian nucleus/nucleus ventro-oralis internus (CM-Voi)
- 正中神经电刺激术 medianus nerve stimulation (MNS)
- 植入式脉冲发生器 implantable pulse generator (IPG)
- 植物状态/无反应觉醒综合征
vegetative state/unresponsive wakefulness syndrome (VS/UWS)
- 质量调整生命年 quality adjusted life year (QALY)
- 中国泌尿外科学会 Chinese Urological Association (CUA)
- 中型多棘神经元 medium spiny neurons (MSNs)
- 终纹床核 bed nucleus of stria terminalis (BNST)
- 肿瘤坏死因子- α tumor necrosis factor- α (TNF- α)
- 重度难治性抑郁症 treatment-resistant depression (TRD)
- 周围神经电刺激术 peripheral nerve stimulation (PNS)
- 自适应脑深部电刺激术
adaptive deep brain stimulation (aDBS)
- McLeod 综合征 McLeod syndrome (MLS)
- 组织激活体积 volume of tissue activated (VTA)
- 最小意识状态 minimally conscious state (MCS)