

· 综述 ·

非侵入性脑刺激技术在单侧空间忽略治疗中的应用进展

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单侧空间忽略(unilateral spatial neglect, USN)又被称为半侧空间忽略(hemispatial neglect, HN),其在脑卒中人群内的发病率约为 30%^[1]。USN 是一种神经功能障碍综合征,表现为患者无法意识到病灶对侧空间内的事物,不能对该空间内的事物作出正确的定向、反应及加工^[2]。目前常用的治疗方法包括常规作业训练、视动训练、颈部振动、前庭刺激(冷/热水)、半边透光眼镜、棱镜适应等^[3]。但上述方法还不足以彻底治愈 USN,临床也尚未制订 USN 的标准化治疗方案^[4]。近年来,随着非侵入性脑刺激技术(noninvasive brain stimulation, NIBS)的发展,有部分研究利用重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)和经颅直流电刺激(transcranial direct current stimulation, tDCS)治疗 USN,取得了一定疗效^[5]。本研究就目前 NIBS 在 USN 治疗中的应用进展综述如下。

USN 的发病机制

皮质结构主要有右顶下小叶、右顶颞交界区、右前额叶、右基底核、丘脑、扣带回等^[6]。目前,USN 的发病机制尚未明确,推测可能与空间注意力相关的神经结构损伤有关,导致注意力分离性损伤、大脑半球连接区域病理改变、内部空间表征失真、空间参考框架偏差及扫视记忆不足等^[7-9]。有研究报道^[10],利用 5Hz 的 rTMS 进行虚拟损害测试,发现其所产生的损害与病理性脑损伤不同,此种损害具有暂时性、可逆性,且其生物学效应可维持一段时间,表明视空间注意认知在两侧大脑半球呈不对称性分布,且右侧半球优势较为明显,即在两侧大脑半球间存在方向性注意的竞争抑制,右侧大脑半球的后顶叶皮质可能是空间定向的关键区域,而右侧额叶皮质可能是执行功能的关键区域。

USN 的 NIBS 治疗

利用 NIBS 治疗 USN 的理论依据是基于方向性注意假说,该假说认为正常两侧大脑半球通过互相抑制达到维持方向性注意平衡的目的,一侧大脑半球受损将会使患侧对健侧的抑制作用降低,导致健侧大脑半球出现病理性过度兴奋,从而引发 USN 症状^[11]。NIBS 具有调节皮质兴奋性的作用,利用其治疗 USN,可重新建立两侧大脑半球间的功能平衡。在此将重点阐述 rTMS、 θ 节律刺激(theta burst stimulation, TBS)、tDCS 等治疗手段对 USN 的疗效影响。

一、rTMS

rTMS 是一种可调节大脑皮质兴奋性的无痛、无创技术,其

将一定强度的时变磁场作用于大脑皮质的相应区域,将其产生的感应电流作用于皮质神经元和突触^[12]。rTMS 能影响局部和远隔皮质功能,实现神经网络重建,影响多种神经递质和基因表达^[13]。研究证实,低频刺激(≤ 1.0 Hz)能降低受刺激结构的兴奋性,可作用于未受损皮质,高频刺激(> 1.0 Hz)能提高受刺激结构的兴奋性,可作用于患侧皮质^[14]。根据作用时程的长短,rTMS 效应可分为即刻效应、中时程效应和长时程效应^[15]。临床研究中,对患者健侧大脑皮质进行治疗时大多采用低频 rTMS,其机理是通过抑制健侧皮质的过度兴奋,从而改善 USN 症状。

(一)低频 rTMS 对大脑皮质兴奋性调节效应的影响

Koch 等^[16]对 12 例右脑损伤伴 USN 的患者和 8 例右脑损伤未伴 USN 的患者进行了研究,按照国际脑电图 10-20 系统(electroencephalograph 10-20, EEG 10-20)标准,在受试者健侧大脑的 P3 点给予 1.0 Hz、90% 静息运动阈值(resting motor threshold, RMT)、共 600 次脉冲的 rTMS,治疗前、后检测患者健侧皮质兴奋性,发现健侧大脑皮质兴奋性过度增高的现象主要存在于伴 USN 症状的患者中,且低频 rTMS 可以有效地降低健侧大脑皮质兴奋性,对未伴 USN 患者的健侧大脑皮质兴奋性尚无显著影响。该研究仅仅对治疗后的即时效应进行了观察,对改善 USN 患者的皮质兴奋性有无维持效应尚不能明确。

(二)低频 rTMS 对 USN 患者忽略症状的改善作用

Song 等^[17]对脑卒中后 15 d 至 60 d 内的 USN 患者进行了研究,在其 P3 点给予 0.5 Hz、90% 运动阈值(motor threshold, MT)、每串 450 次脉冲、共 20 串的 rTMS 治疗,结果显示治疗后及治疗 2 周后刺激组患者的划销试验和直线二等分试验均较治疗前有明显改善,且疗效可维持 2 周。Shindo 等^[18]选取 2 例患者,在其 P5 点给予 0.9 Hz、95% MT、每串 900 次脉冲、共 6 串的 rTMS 治疗,研究结果显示至少需经过 2 周 rTMS 治疗才会使行为性忽略测试结果(behavioral inattention test, BIT)得以改善,其效果可维持 6 周。上述研究均证实 rTMS 对 USN 症状的改善有维持效应,可为临床治疗提供指导。但 2 种研究在起效时间上存在分歧,推测其原因可能是因为刺激位点、刺激参数及评价指标的选择具有差异性,且 Shindo 等所选取的病例为脑卒中慢性期患者,功能恢复较为缓慢,病例数较少,小样本数据无法精确反映出 rTMS 的实际疗效。

(三)高频 rTMS 对 USN 患者忽略症状的改善作用

大多数临床研究从治疗安全角度出发,在患者健侧大脑半球采用低频、长刺激串的 rTMS,防止诱发癫痫发作,而实际上高频 rTMS 诱发癫痫的发生率也非常低。Kim 等^[19]选取 27 例脑卒中急性期的 USN 患者,采用随机双盲对照方法研究健侧后顶叶皮质区(posterior parietal cortex, PPC)低频 rTMS 和患侧 PPC 高频 rTMS 对 USN 疗效的影响,治疗前、后采用直线二等分试验、划销试验、凯瑟琳-波哥量表(Catherine-Bergego scale, CBS)对忽略症状和日常活动能力进行评价,其中 CBS 量表包括与日

DOI:10.3760/cma.j.issn.0254-1424.2014.010.021

基金项目:江苏省“六大人才高峰”项目(N2011-WS-100);江苏省卫生计生厅工程重点学科基金(XK20200903)

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常生活活动 (activities of daily living, ADL) 能力密切相关的 10 个项目,如穿衣、洗漱、吃饭、交流、移动等,结果显示各组 CBS 评分改善均不明显,提示高频 rTMS 可有效改善脑卒中急性期患者的患侧忽略症状。分析认为研究中 CBS 改善不明显的原因可能是因为该评分与 ADL 密切相关,包含了对疾病及自身空间的认知,但治疗中缺乏与 ADL 能力和疾病认知相关的训练,因此提高 CBS 评分较为困难。

二、TBS

TBS 是一种模式化 rTMS,按照间隔时间不同,TBS 可分为间歇性 TBS (intermittent TBS, iTBS) 和连续性 TBS (continuous TBS, cTBS)。iTBS 对刺激结构起兴奋作用,主要作用于患侧大脑皮质,cTBS 对刺激结构起抑制作用,主要作用于健侧大脑皮质^[20]。与传统 rTMS 比较,TBS 在 20~190 s 内即可引发皮质兴奋性的改变,缩短了约 20 min 的刺激时间^[21]。目前的临床研究大多倾向于在患者健侧大脑皮质应用 cTBS。

(一) cTBS 对 USN 患者忽略症状的改善作用

Koch 等^[22]采用随机双盲对照方法,在患者健侧 PPC 给予 2 周的 cTBS 治疗,治疗参数为 100% RMT、脉冲 3 次、串刺激间隔 44 s,801 次脉冲,治疗前、后对患者进行 BIT 评估,BIT 包括 15 个项目,其中包括 6 项纸笔测试(直线划销、字母划销、星型划销、线段二等分、图片临摹、自由绘图)和 9 项行为学测试(图片扫视、打电话、读菜单、读文章、告诉并设定时间、硬币分类、抄写地址和句子、地图导航、卡片分类)^[23]。结果显示刺激组 BIT 较治疗前明显改善,刺激 2 周时 BIT 分值增高 16.3%,4 周后 BIT 分值增高 22.6%,提示 cTBS 可以改善患者患侧的忽略症状,且治疗效果可维持较长时间,由此推测除即刻效应外,cTBS 治疗 USN 还可能与神经网络重建的长时程效应有关。由于 BIT 无自身空间测试,所以并不能准确反映患者自身空间忽略的改变情况。

(二) cTBS 对 USN 患者 ADL 能力的改善作用

Cazzoli 等^[24]采用随机双盲对照方法,将平均病程为 26.63 d 的 24 例右利手脑卒中后伴 USN 患者分为 3 组:先 cTBS 后假刺激组、先假刺激后 cTBS 组和无刺激对照组。采用文献^[22]中的治疗参数对患者的 P3 点进行刺激,治疗前、后对患者进行常规纸笔测试和 ADL 能力评估,发现先 cTBS 后假刺激组和先假刺激后 cTBS 组患者的忽略症状、ADL 能力均较治疗前有所改善,其疗效可维持至刺激后 3 周,提示 cTBS 不仅对 USN 患者的忽略症状有改善作用,对其 ADL 能力恢复也有积极作用。

三、tDCS

tDCS 是一种 NIBS,通过放置在头皮的 2 个电极,利用微电流(1~2 mA)调节大脑皮质的兴奋性^[25]。与 rTMS 相比,tDCS 的电极片面积较大(25~35 cm²),产生的效应较 rTMS 更为广泛^[26]。tDCS 的效应主要依赖于刺激部位、极性、电流强度等因素,当阳极靠近神经元胞体或树突时,神经元放电增加,当阴极靠近神经元胞体或树突时,神经元放电减少,提示阳极刺激可提高神经元的兴奋性,增强皮质活动,阴极刺激可降低神经元刺激性,抑制皮质活动^[27]。

(一) tDCS 对大脑皮质兴奋性调节效应的影响

Medina 等^[28]在健康受试者 PPC 区进行 tDCS,探讨其是否可能对受试者的视觉空间功能造成影响,该研究将受试者分为右

侧阴极左侧阳极刺激组、右侧阳极左侧阴极刺激组和假刺激组,结果发现在右侧阴极左侧阳极刺激组可以模拟出“局灶性损伤”模型,继而引发相应的 USN 症状,右侧后顶叶皮质区的功能抑制导致左侧半球相应功能增强,引起两大半球功能失衡,其作用机制与 rTMS 相似,由此推断,tDCS 对皮质兴奋性有调节效应,可以治疗视觉空间障碍,是 USN 的有效治疗技术。

(二) tDCS 对 USN 患者忽略症状的改善作用

Sparing 等^[29]用电流强度为 1 mA 的 tDCS 治疗 10 例 USN 患者,其平均病程为(2.9±3.5)个月,治疗时,分别在患者的 P3 点应用阳极 tDCS、P3 点应用阴极 tDCS、P4 点应用阳极 tDCS、P4 点应用假刺激,结果显示,在 P4 点使用阳极 tDCS 可以明显改善注意表现成套试验(test battery of attentional performance, TAP)评分,在 P4 点使用阳极 tDCS 和 P3 点使用阴极 tDCS 可以明显改善直线二等分试验评分。Ko 等^[30]对 15 例脑卒中后 USN 患者进行测试,在 P4 点使用 2 mA 的阳极 tDCS,治疗时间为 10 min,结果发现,治疗后患者的划销试验和直线二等分试验评分明显改善。上述研究的观察重点均为即刻效应,忽略了对后续效应的观察,因此并不能明确 tDCS 的有效时程,也不能证明多次 tDCS 能否形成累加效果。

NIBS 治疗 USN 的安全性

目前,传统模式 rTMS 的主要不良反应是高频易诱发癫痫样发作,其长期不良反应尚鲜见报道^[31]。国际 TMS 研讨会在重新修订的《国际重复性经颅磁安全协会的应用指南》中指明,若在安全范围内选择刺激参数,高频 rTMS 治疗的安全性可得到保证^[32]。有研究报道,低频 rTMS 可治疗癫痫发作^[33]。Oberman 等^[34]在健康人群的 M1 区应用丛内频率 50 Hz、串刺激间隔 200 ms、共 150 个脉冲、强度 100% RMT 的 cTBS,发现测试中有 1 例受试者出现癫痫样发作。TBS 的不良反应主要为头部和面部疼痛、肌肉收缩等^[35]。临床治疗中,从 rTMS 治疗的安全角度出发,有癫痫病史、服用过易致癫痫发作药物或颅内金属植入物的患者禁用。与 rTMS 不同的是,tDCS 影响的只是处于活动状态的神经元,不会使处于休眠状态的神经元产生放电。目前,有关 tDCS 可诱发癫痫发作的报道尚较为鲜见。有研究报道,给予癫痫患者阴极 tDCS 刺激后,其癫痫样放电计数明显减少^[5]。因此,tDCS 的应用相对更安全。

在认知方面,有研究采用神经功能缺损量表(National Institute of Health stroke scale, NIHSS)和简易智能状态检查量表(mini-mental status examination, MMSE)探讨低频 rTMS 对 USN 患者视空间障碍及认知功能有无消极影响,结果显示所有受试者均未出现负性得分^[36]。有研究指出^[37-38],接受 tDCS 的受试者在刺激后并未出现大脑组织水肿、血脑屏障失衡、脑组织结构改变等现象,由此推断,tDCS 对受试者的认知功能无负性影响。

总结与展望

NIBS 可直接、安全地调节大脑皮质兴奋性,是研究大脑神经可塑性和功能重建的重要方法之一,拥有较好的应用前景。USN 的病理机制与半球间的竞争抑制有关,在临床工作中可选择不同方案的 NIBS 予以治疗,然而,NIBS 治疗 USN 的最佳临床治疗方案(如刺激频率、部位、强度、时间、极性)尚未确定,

仍需进一步细化刺激参数。目前,有关临床治疗的文献报道大多都是小样本研究,在今后的研究中仍需扩大样本量。此外,在常规康复方法上联合 NIBS 治疗 USN 的临床疗效也需进一步观察,以便更好地将其应用于 USN 患者的临床治疗中。

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(修回日期:2014-06-18)

(本文编辑:凌 琛)

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Heparin versus aspirin for preventing early neurologic deterioration

BACKGROUND AND OBJECTIVE Early neurologic deterioration (END) and is a common event among patients with acute stroke. This study was designed to determine whether anticoagulation with low molecular weight heparin (LMWH) is superior to treatment with aspirin in preventing END in patients with acute ischemic stroke.

METHODS This prospective study included 1,360 patients with first-ever ischemic stroke. The subjects were randomly assigned to receive either enoxaparin twice per day or aspirin at 200 mg once per day for 10 days. Both groups then received aspirin, 100 mg daily for six months. All participants underwent a brain CT scan before randomization and a second scan at 10 days. Baseline data collected, included demographics, medical history, modified Rankin scale (mRS), and NIHSS scores. At day 10, trained personnel determined the NIHSS and mRS scores. The primary endpoints were the occurrence of END, Early recurrent ischemic stroke (ERIS), venous thromboembolism or myocardial infarction at 10 days post-admission. END was defined as an increase of four or more points on the NIHSS scale.

RESULTS Of the 1,368 patients, 7.89% suffered from END. There was a significant reduction in the frequency of END among those in the low molecular weight heparin group as compared with the aspirin group ($P < 0.001$). At 6 months, there was a significant difference in the frequency of good outcomes among patients over the median age of 70 years ($P < 0.001$), as well as in patients with symptomatic stenosis of the posterior circulation ($P < 0.01$) and basilar artery ($P < 0.01$). Those in the low molecular weight heparin group had a lower frequency of DVT during the first 10 days than did the aspirin group ($P = 0.003$). There was no difference between groups in ERIS.

CONCLUSION This study of patients with ischemic stroke found that treatment with low molecular weight heparin within 48 hours of stroke until day 10 may reduce early neurologic deterioration.

【摘自:Yi X, Lin J, Wang C, et al. Low molecular weight heparin is more effective than aspirin in preventing early neurologic deterioration and improving six-month outcome. *J Stroke Cerebrovasc Diseases*, 2014, 23(6): 1537-1544.】

Total hip replacement among patients with osteoarthritis and rheumatoid arthritis

BACKGROUND AND OBJECTIVE Over 50% of patients with rheumatoid arthritis (RA) have reported orthopedic procedures. The outcomes of total hip replacement among patients with RA are not well described. This study assessed pain, function and quality-of-life two years after hip replacement, comparing patients with RA and those with osteoarthritis (OA).

METHODS Data were reviewed concerning patients undergoing total hip replacement between 2007 and 2011. From these data, the authors identified patients receiving hip replacements due to RA or OA. Data collected included demographic information, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the SF-12v2 Short Form Health Survey, comorbidities and the American Society of Anesthesia Score.

RESULTS The analysis included 5,473 patients with OA and 193 with RA. Similar proportions of patients with RA and with OA had clinically significant improvements in function, although patients with RA had significantly worse WOMAC function at two years ($P < 0.001$). Patients with RA had worse preoperative WOMAC pain scores ($P < 0.001$) and worse WOMAC pain scores at two years ($P < 0.001$) than did patients with OA.

CONCLUSION This study of patients undergoing total hip replacement found that those with RA continued to experience worse WOMAC pain and function two years after total hip replacement than did those with OA.

【摘自:Goodman SM, Ramsden-Stein DN, Huang WT, et al. Patients with rheumatoid arthritis are more likely to have pain and poor function after total hip replacements than patients with osteoarthritis. *J Rheum*, 2014, 41(9): 1774-1780.】