·临床研究·

低频重复经颅磁刺激对卒中后抑郁的远期疗效及血浆 5-羟色胺表达的影响

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【摘　要】 **目的**　探讨低频重复经颅磁刺激(rTMS)对卒中后抑郁的远期效应及血浆 5-羟色胺(5-HT)表达的影响。**方法**　选取 74 例符合本研究标准的脑卒中后抑郁(PSD)患者,按随机数字表法分成对照组(35 例)和治疗组(39 例)。最终资料完整纳入本研究患者 65 例,对照组 31 例,治疗组 34 例。对照组给予舍曲林及基础治疗,治疗组给予低频 rTMS 及基础治疗,疗程 8 周。分别于入组前(治疗前)和治疗 8 周后(治疗后),采用汉密尔顿抑郁量表(HAMD)、中国脑卒中量表(CSS)及改良 Barthel 指数(MBI)等指标来评定患者的临床抑郁状态、临床神经功能缺损程度及日常生活活动(ADL)能力;以高效液相色谱法检测 2 组患者治疗前后血浆 5-HT 浓度。并于 12 个月后追踪随访(随访时),复测上述指标,进行统计学分析比较。**结果**　治疗后,2 组患者 HAMD 评分和 CSS 评分均较治疗前明显下降($P<0.05$),MBI 评分则较治疗前明显提高($P<0.05$);但 2 组间比较,差异无统计学意义($P>0.05$);对照组血浆 5-HT 浓度较治疗前明显升高($P<0.05$),但治疗组变化不明显($P>0.05$)。12 个月后随访时,2 组患者 HAMD 评分和 CSS 评分均较治疗后进一步下降($P<0.05$),MBI 评分亦进一步提高($P<0.05$);2 组间比较,治疗组较对照组 HAMD 评分下降及 MBI 评分提高更为显著($P<0.05$);2 组患者血浆 5-HT 浓度较治疗后稍高,但差异无统计学意义($P>0.05$)。治疗后,对照组和治疗组脱离抑郁状态患者分别有 10 例(32.26%)和 12 例(35.29%),差异无统计学意义($\chi^2=0.067$, $P=0.796$),但 12 个月后随访时,2 组脱离抑郁状态患者分别有 22 例(70.97%)和 31 例(91.18%),组间差异有统计学意义($\chi^2=4.399$, $P=0.036$)。**结论**　rTMS 治疗可以改善脑卒中后抑郁患者的远期效应,提高患者 ADL 能力,且其作用机制可能与血浆 5-HT 表达变化无关。

【关键词】 经颅磁刺激,低频重复;　卒中后抑郁;　远期效应;　5-羟色胺;　日常生活活动

The effect of low-frequency repetitive transcranial magnetic stimulation on post-stroke depression and the expression of plasma 5-hydroxytryptamine

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【**Abstract**】 **Objective**　To explore any effect of low-frequency transcranial magnetic stimulation (rTMS) on post-stroke depression and the expression of plasma 5-hydroxytryptamine (5-HT). **Methods**　Seventy-four patients suffering from post-stroke depression (PSD) were divided into a control group (31 cases) which received basic therapy and sertraline and a therapy group (34 cases) which received basic therapy and 8 weeks of low-frequency rTMS. Scores on the Hamilton depression (HAMD) scale and the Chinese stroke scale (CSS) and the modified Barthel index (MBI) were used to evaluate depression, neurological impairment, and ability in the activities of daily living (ADL) before and after the experiment. Levels of plasma 5-HT in the two groups were also detected with high performance liquid chromatography before and after the experiment. The patients were then followed up 1 year later, when these indexes were reassessed. **Results**　After 8 weeks of treatment the HAMD and CSS scores in both groups had decreased significantly, and their MBI scores had increased significantly compared with prior to treatment, but there was no significant difference between the groups. The average plasma 5-HT concentration in the control group had increased significantly, but there was little change in the therapy group. One year later, the HAMD and CSS scores of both groups had declined significantly and their MBI scores had increased further. The average decrease in HAMD scores and rise in MBI scores in the therapy group was significantly greater

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than in the control group. There had been no significant change in plasma 5-HT concentration in either group. After 8 weeks of treatment, 10 controls and 12 therapy group patients had escaped depression. A year later the numbers were 22 and 31 cases, a significant inter-group difference. **Conclusion** Low-frequency rTMS can help alleviate post-stroke depression, and enhance ADL ability. The mechanism might have nothing to do with any change in 5-HT expression.

【Key words】 Transcranial magnetic stimulation; Post-stroke depression; 5-hydroxytryptamine; Activities of daily living

脑卒中后抑郁(post-stroke depression, PSD)是脑卒中后常见的情感障碍之一,患病率约 30% ~ 50%[1],严重影响患者神经功能的康复。目前 PSD 病理机制尚不明确,可能与前额叶皮质下回路等区域及脑内生物胺类递质或受体等代谢改变有关。临床上常用单胺氧化酶抑制剂、三环类抗抑郁药或选择性 5-羟色胺(5-hydroxytryptamine, 5-HT)再摄取抑制剂等治疗,由于药物不良反应多及患者依从性差,影响了药物的广泛使用[2]。近年来,重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)广泛应用于临床,研究证实,合理参数的 rTMS 对帕金森病、重症抑郁及精神分裂症等有显著效果[3-4]。本研究选择 PSD 患者作为研究对象,治疗组采用低频 rTMS 治疗,对照组以目前常用的选择性 5-HT 再摄取抑制剂——舍曲林口服抗抑郁治疗,对比观察低频 rTMS 对 PSD 的近期疗效及远期效应,并检测血浆 5-HT 表达水平,旨在探讨低频 rTMS 治疗 PSD 患者的可能机制。

资料与方法

一、研究对象及分组

入选标准:①符合 1995 年中华医学会第 4 届脑血管病学术会议修订的脑卒中诊断标准[5];②神志清楚,病情稳定;③病程 > 0.5 个月;④有神经功能缺损症状和体征,中国脑卒中量表(China stroke scale, CSS)[5]评分在 16 ~ 30 分;⑤汉密尔顿抑郁量表(Hamilton depression scale, HAMD)[6]评分≥8 分;⑥听力理解正常,简易精神状态检测表(mini-mental state examination, MMSE)[7]评分 > 20 分;⑦入选前半个月内未服用苯二氮卓类药物史;⑧签署患者知情同意书。

排除标准:①重症抑郁或自杀倾向;②脑出血倾向;③头部或者心脏安装有金属物体;④不稳定型心绞痛者;⑤合并恶性肿瘤者;⑥住院期间病情逐渐恶化;⑦中重度吞咽或言语障碍;⑧不能配合及耐受者;⑨随访期间再发脑卒中,或其它重大疾病。本研究获本院医学伦理委员会批准。

选取 2010 年 9 月至 2012 年 5 月本院收治且符合上述标准的脑卒中后抑郁患者 74 例。根据患者治疗方法的不同,按随机数字表法分为对照组(35 例)和治疗组(39 例)。由于本研究需观察远期效应, 3 例患者因头痛未完成本研究,6 例因失访,故剔除,最终资料完整纳入本研究患者 65 例,对照组 31 例,治疗组 34 例。2 组患者性别、年龄、病程、服药史和病情等一般临床资料经统计学分析比较,差异无统计学意义($P > 0.05$),具有可比性,详见表 1。

二、治疗方法

对照组给予舍曲林口服及基础治疗,治疗组给予低频 rTMS 及基础治疗。共治疗 8 周。

1. 舍曲林口服药物治疗:开始 50 mg 口服,每日 1 次,1 周后加至 100 mg 维持,第 6 周时减量至 50 mg,第 7 周减至 25 mg,疗程 8 周。

2. 低频 rTMS 治疗:rTMS 仪器由丹麦 MagVenture 公司生产,型号为 MagPro X-100;采用丹麦 Keypoit 肌电图仪测试运动诱发电位。患者取仰卧位或者半卧位,闭目,磁刺激线圈对准左前额叶背外侧区,距离头皮切面 0.5 cm,强度为 80% 运动阈值(motor threshold, MT),频率 1 Hz,每序列 50 个脉冲,序列间隔 5 s,每次 30 个序列 28 min,每日 1 次,1 周 5 次;每 2 周重新测定运动阈值,调整治疗强度。每次治疗过程中观察患者反应,治疗结束时询问有无不适。疗程 8 周。

3. 基础治疗:根据患者患有基础疾病的不同,分别行相应的降血压、降血糖、降血脂、抗血小板聚集或抗凝等治疗,行脑卒中二级预防;根据功能障碍的分类及程度,分别安排主、被动关节活动度训练,坐站平衡训练,治疗性步态训练及日常生活活动(activities of daily

表 1　2 组患者间一般资料比较

组别	例数	性别(例)		平均年龄(岁, $\bar{x} \pm s$)	平均病程(d, $\bar{x} \pm s$)	服药史(例)				脑梗死(例)	MMSE 评分(分)
		男	女			服降压药	服降糖药	服抗血小板聚集药	服降脂药		
对照组	31	19	12	57.71 ± 9.94	25.35 ± 8.31	21	11	12	21	13	27.26 ± 2.38
治疗组	34	25	9	60.94 ± 10.42	28.68 ± 10.76	19	9	15	25	17	26.03 ± 2.75

living, ADL)能力训练等,有言语或吞咽功能障碍者,亦给予相应治疗。

根据本地医保制度(病情稳定,28 d 内不能以同一疾病再次入院),结合患者功能障碍的程度及经济状况,出院后 10 个月之内,每例患者每 2 个月住院 1 次,住院期间均未再行 rTMS 或其它抗抑郁治疗,但维持基本治疗内容。患者回归家庭期间自行功能锻炼。

三、疗效评定方法

1. 评定指标:所有患者于入组前(治疗前)、治疗 8 周后(治疗后)及治疗后 12 个月(随访时)分别采用 HAMD 评分、CSS 评分及改良 Barthel 指数(Barthel index, MBI)[8]等指标对 2 组患者的临床抑郁状态、临床神经功能缺损程度及 ADL 能力进行评定。其中,HAMD 评定采用 17 项版本[6], >24 分为重度抑郁,21 ~24 分为中度抑郁,8 ~20 分为轻度抑郁, <8 分为正常。

2. 血浆 5-HT 检测:所有患者于治疗前、治疗后及随访时空腹抽血,以高效液相色谱法检测血浆 5-HT 浓度。此操作由检验科医师完成。

3. 疗效标准:根据抑郁状态的诊断标准,将患者 HAMD 评分 <8 分设为脱离抑郁状态,即治愈。以上所有评定由经过专业培训的康复医师完成。

四、统计学处理

采用 SPSS 16.0 版统计软件进行统计学分析,计量资料用($\bar{x} \pm s$)表示,2 组均数间的比较采用两独立样本 t 检验,治疗前后均数间的比较采用配对 t 检验;计数资料的比较采用 χ^2 检验。$P<0.05$认为差异有统计学意义。

结　果

一、2 组患者治疗前后各评定指标及 5-HT 浓度比较

治疗 8 周后(治疗后),2 组患者 HAMD 评分和 CSS 评分均较治疗前有明显下降($P<0.05$),MBI 评分较治疗前明显提高($P<0.05$);但 2 组间同时间点比较,差异均无统计学意义($P>0.05$)。治疗后 12 个月随访时,2 组患者 HAMD 评分和 CSS 评分均较治疗 8 周后进一步下降($P<0.05$),MBI 评分也较治疗 8 周后进一步提高($P<0.05$);而治疗组 HAMD 评分下降较对照组更为明显,MBI 评分提高也较对照组更为明显,两组组间比较,差异均有统计学意义($P<0.05$);但随访时 CSS 评分组间比较,差异无统计学意义($P>0.05$)。详见表 2。

治疗后,对照组血浆 5-HT 浓度较治疗前升高,差异有统计学意义($P<0.05$),但治疗组变化不明显($P>0.05$);12 个月后随访时,2 组血浆 5-HT 浓度均较治疗后稍有升高($P>0.05$),2 组间差异亦无统计学意义($P>0.05$)。详见表 2。

二、2 组患者治疗后抑郁状态变化比较

治疗 8 周后,对照组和治疗组脱离抑郁状态患者分别有 10 例(32.26%)和 12 例(35.29%),2 组差异无统计学意义($\chi^2=0.067$, $P=0.796$);但 12 个月后随访时,2 组脱离抑郁状态患者分别达 22 例(70.97%)和 31 例(91.18%),组间比较,差异有统计学意义($\chi^2=4.399$, $P=0.036$)。

讨　论

近 30 年来,治疗抑郁症的经典药物有单胺氧化酶抑制剂和三环类抗抑郁药,临床上常选用选择性 5-HT 再摄取抑制剂,疗效肯定[9]。但由于药物的不良反应及患者依从性差,影响了口服药物的广泛使用,致使很多患者长期处于抑郁状态。而 rTMS 是近 20 年来发展起来的新的神经电生理技术,根据磁信号转变为电信号的原理,刺激能改变大脑局部及远隔皮质多种基因及神经递质表达,实现区域性功能重建,最终影响言语、认知、情绪及肢体运动等功能,目前广泛应用于临床[3,4,10]。目前尚未见有关 rTMS 对 PSD 的远期效应的研究报道。

本研究选取一组 PSD 患者作为研究对象,对比观察(抗抑郁药物)对照组和(rTMS 疗法)治疗组对应治疗后的近期效果(治疗 8 周后)和远期效应(治疗 12 个月后随访时)。结果显示,治疗 8 周时,2 组患者的 HAMD 和 CSS 评分均较治疗前明显下降,但两组之间降低幅度差异并无统计学意义($P>0.05$),提示低频

表 2　2 组患者治疗前后各评定指标及 5-HT 浓度比较($\bar{x} \pm s$)

组别	例数	HAMD 评分(分)			CSS 评分(分)		
		治疗前	治疗后	随访时	治疗前	治疗后	随访时
对照组	31	17.35 ±5.70	10.58 ±4.79[a]	6.06 ±3.43[ab]	21.19 ±4.60	15.90 ±3.98[a]	11.06 ±2.83[ab]
治疗组	34	16.79 ±5.20	9.38 ±4.83[a]	4.50 ±2.50[abc]	23.03 ±4.67	17.41 ±4.37[a]	11.68 ±3.90[ab]
组别	例数	MBI 评分(分)			5-HT(ng/ml)		
		治疗前	治疗后	随访时	治疗前	治疗后	随访时
对照组	31	38.39 ±9.94	53.23 ±8.71[a]	70.48 ±6.37[ab]	45.44 ±19.58	47.75 ±19.82[a]	48.62 ±18.82[a]
治疗组	34	40.29 ±11.41	55.74 ±10.38[a]	74.56 ±9.40[abc]	50.00 ±21.51	50.89 ±19.99	51.21 ±22.24[a]

注:与组内治疗前比较,[a]$P<0.05$;与组内治疗后比较,[b]$P<0.05$;与对照组同时间点比较,[c]$P<0.05$

rTMS具有与舍曲林同等的短期抗抑郁效应。本组研究对象多为轻度至中度抑郁,随着患者肢体运动功能及ADL能力的改善,抑郁状态亦会相应减轻。二者之间是相互影响、相互联系的。

本研究12个月后追踪随访,2组患者的HAMD评分均较8周时进一步下降;在此期间,2组患者均未再口服抗抑郁药或rTMS治疗。其抑郁改善可能与患者情绪障碍的自我修复或肢体功能的康复对情绪障碍的正面影响等多因素有关。进一步分析发现,治疗组较对照组HAMD评分下降更明显,提示低频rTMS抗抑郁作用的远期效应可能优于舍曲林。本研究结果还显示,治疗组MBI评分升高幅度也明显超过对照组,但2组间CSS评分降低幅度无明显差异,后者可能与脑卒中后神经功能的康复在一定时期达到平台期有关,而ADL能力的改善不完全依赖于患侧肢体的运动功能,健侧肢体的代偿会发挥一定作用。所以,rTMS对PSD患者远期ADL能力的影响机制复杂,而抑郁状态的改善致患者正性情绪增加可能是内源性动力机制之一。

根据抑郁状态的诊断标准,本研究显示,治疗8周时2组患者脱离抑郁状态比率无明显差别,可12个月后治疗组(91.18%)脱离抑郁状态的比率明显高于对照组(70.97%),差异有统计学意义($P<0.05$)。这再次说明低频rTMS抗抑郁作用的远期效应优于舍曲林。

情绪障碍的病理机制非常复杂,神经生化、神经免疫及神经内分泌等均参与其发生发展[11],至今尚未完全阐明,其中,以神经生化的单胺类神经递质假说最为认可。5-HT作为一种抑制性神经递质,参与多种中枢神经活动,在调节睡眠、控制情绪、进食、学习、记忆、甚至性行为等方面均发挥重要作用[12-15]。当机体应激时,5-HT及其受体表达异常或功能下降,均可促发情绪障碍疾病的发生。rTMS治疗抑郁状态疗效肯定[16],但是否与5-HT表达异常相关,尚无相关报道。有学者认为,外周血神经递质可反映脑中神经递质水平,检测其外周血表达量可间接反映脑内情况[17]。但也有学者持反对观点,认为血脑屏障的存在及对神经递质的极低通透性,限制了神经递质的转运,所以外周血递质水平不能准确反映脑内递质改变[18]。

本研究对比观察2组患者不同时程血浆5-HT浓度,结果显示,治疗8周时,对照组血浆5-HT浓度较治疗前显著升高($P<0.05$),但rTMS治疗组变化不明显($P>0.05$);12个月后随访,2组血浆5-HT浓度均较8周时稍高,但组间差异无统计学意义($P>0.05$)。结合2组患者抑郁状态的变化,分析如下:治疗8周前,对照组一直口服舍曲林,其作为5-HT再摄取抑制剂,可自由通过血脑屏障,除抑制中枢神经对5-HT的再摄取外,还具有抑制外周血小板对5-HT的再摄取,从而使血浆5-HT浓度升高;而在8周至12个月,对照组未再服用舍曲林,血浆5-HT浓度与8周时比较也无明显变化,但HAMD评分较8周时进一步下降,这说明患者抑郁状态的改善可能不依赖于血浆5-HT浓度变化;这也间接证明,8周前患者血浆5-HT浓度变化为舍曲林的外周效应所致。重要的是,本研究发现rTMS治疗组的血浆5-HT浓度自始至终未发生明显变化,提示rTMS的抗抑郁效应亦不依赖于血浆5-HT浓度变化。故认为,血浆5-HT浓度不能作为抑郁状态治疗效果的评定标准。

综上所述,低频rTMS可以改善PSD患者的远期效应,提高ADL能力,其机制可能与血浆5-HT表达变化无关。当然,本研究也存在以下问题:①rTMS治疗费用较高,医疗成本增加,难以广泛开展,故大样本的病例收集存在困难;②患者出院后的自主运动量、家庭环境、亲情支持等多因素不易控制,可能对最终结果造成潜在影响;③由于医学伦理问题,人类脑脊液与脑组织相关神经递质及受体的检测不能开展。所以,PSD动物模型的建立将会有助于低频rTMS抗抑郁机制的进一步探讨。

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· 外刊撷英 ·

Door to needle time for ischemic stroke

BACKGROUND AND OBJECTIVE Intravenous tissue plasminogen activator (tPA) has been found to reduce long-term disability in patients with acute ischemic stroke, although these benefits are highly time dependent. However, prior studies have demonstrated that less than one third of patients presenting with acute ischemic stroke in the United States are treated within the guideline recommended timeframe. This study sought to better understand the effect of door to needle time on clinical outcomes.

METHODS Data were collected as part of the Target Stroke Quality Improvement Initiative launched in January of 2010 to address the shortfall in providing timely acute ischemic stroke care. The primary goal of the initiative was to administer tPA to at least 50% of the patients with acute ischemic stroke within 60 minutes of hospital arrival. Strategies included prenotification of hospitals by emergency medical services personnel, activating the entire stroke team with a single call or page, rapid acquisition and interpretation of brain imaging, use of specific protocols and tools, premixing tPA for high-likelihood candidates, a stroke team-based approach and rapid feedback to the stroke team regarding performance.

RESULTS A total of 71,169 patients with acute ischemic stroke were identified for study analysis. The median age of the sample was 72 years, with 50.1% women. The median door to needle time for tPA administration for the pre-intervention period was 77 minutes, decreasing to 67 minutes in the post-intervention period ($P<0.001$). The percentage of patients with a door to needle time of 60 minutes or less increased from 29.6% to 53.3%. After the initiative, in-hospital mortality for patients with ischemic stroke was less likely ($P<0.001$), while discharge to home was more likely ($P<0.001$).

CONCLUSION This study found that the implementation of a national quality improvement initiative resulted in improved timeliness of tPA administration, resulting in improved hospital mortality, decreased intracranial hemorrhage and increased discharges to home.

【摘自:Fonarow GC, Zhao X, Smith EE, et al. Door to needle time for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA, 2014, 23(30): 1632-1640.】

Large middle cerebral artery stroke and hemicraniotomy

BACKGROUND AND OBJECTIVE Large middle cerebral artery (MCA) infarctions are associated with the development of massive brain edema, which may lead to herniation and early death. This condition has been described as malignant MCA infarction. Decompressive hemicraniotomy, combined with duraplasty, can prevent fatal internal displacement of brain tissue and herniation. This study was designed to test the outcome of early hemicraniectomy compared with intensive care unit (ICU) treatment among patients 61 years of age or older with malignant MCA infarction.

METHODS This prospective, randomized, controlled open trial included patients 61 years of age or older with a diagnosis of acute unilateral MCA infarction, involving at least two thirds of the MCA territory. Subjects were assigned to either treatment in the ICU or early hemicraniectomy. Data were collected during hospitalization and at follow-up visits at six and 12 months. The primary outcome measure was a score of 0 to 4 on the modified Rankin scale at six months.

RESULTS A total of 112 patients were randomized to the study. In the intention to treat sample, survival without severe disability occurred in 38% of the surgery group and 18% of the control group ($P=0.04$). The 12-month survival rates were 57% in the surgery group and 24% in the control group. The intention to treat analysis revealed that all secondary endpoints were significantly better in the surgery group than in the control group. This trial was discontinued for reasons of efficacy after reductions in deaths and severe disability had become significant.

CONCLUSION This study of patients with extensive MCA stroke found that early hemicraniectomy can significantly improve survival, although most survivors had substantial disability.

【摘自:Jüttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in Older Patients with Extensive Middle Cerebral Artery Stroke. N Eng J Med, 2014, 370(12): 1091-1100.】