·神经康复·

重复经颅磁刺激对神经病理性疼痛患者疼痛和情绪的影响

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【摘要】 **目的** 探讨高频重复经颅磁刺激对伴焦虑和(或)抑郁的神经病理性疼痛患者疼痛和情绪障碍的治疗作用。**方法** 纳入2019年6月至2021年10月在空军军医大学西京医院住院治疗的39例伴焦虑和(或)抑郁的神经病理性疼痛患者,随机分为常规治疗并假刺激组(对照组,19例)和常规治疗辅助高频重复经颅磁刺激组(rTMS组,20例);于治疗前及治疗3 d和1、2、3、4周时采用疼痛数字评价量表(NRS)评价疼痛状态、汉密尔顿焦虑量表14项(HAMA-14)评价焦虑状态、汉密尔顿抑郁量表17项(HAMD-17)评价抑郁状态。**结果** rTMS组与对照组治疗前后NRS评分($F=23.573$,$P=0.000$)、HAMD评分($F=15.426$,$P=0.000$)差异有统计学意义,其中rTMS组治疗1、2、3和4周时NRS评分、HAMD评分均低于对照组(均$P\leqslant0.01$)。同一处理组不同观察时间点NRS评分($F=317.751$,$P=0.000$)、HAMA评分($F=81.510$,$P=0.000$)和HAMD评分($F=32.773$,$P=0.000$)差异亦有统计学意义,其中rTMS组治疗1、2、3和4周时NRS评分、HAMD评分均低于治疗前和治疗3 d时(均$P<0.01$),治疗1、2和3周时HAMA评分均低于治疗前和治疗3 d时(均$P=0.000$),治疗4周时HAMA评分低于治疗前($P=0.007$)及治疗1周($P=0.014$)和2周($P=0.001$)时;对照组NRS评分仅治疗4周时低于治疗前($P=0.000$),治疗1、2和3周时HAMA评分均低于治疗前(均$P<0.05$),治疗1周时HAMA评分低于治疗3 d时($P=0.002$)。Spearman秩相关分析显示,疼痛缓解程度与焦虑($r_s=0.442$,$P=0.048$)和抑郁($r_s=0.705$,$P=0.001$)情绪改善呈正相关。**结论** 高频重复经颅磁刺激治疗伴焦虑和(或)抑郁的神经病理性疼痛安全、有效,可在缓解疼痛症状的同时显著改善患者焦虑和抑郁情绪。

【关键词】 神经痛; 经颅磁刺激; 情绪; 康复

Effects of repetitive transcranial magnetic stimulation on pain and emotion of patients with neuropathic pain

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【Abstract】 **Objective** To investigate the effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) on pain and emotion in patients with neuropathic pain (NP) combined with anxiety and/or depression. **Methods** A total of 39 patients with NP combined with anxiety and/or depression from June 2019 to October 2021 were included and randomly divided into conventional treatment combined with sham stimulation group (control group, n = 19) and conventional treatment-assisted high-frequency rTMS (rTMS group, n = 20). The Numerical Rating Scale (NRS) was used to evaluate the pain state, Hamilton Anxiety Scale-14 (HAMA-14) was used to evaluate the anxiety state, and Hamilton Depression Scale-17

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(HAMD-17) was used to evaluate depression state before treatment and at 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks of treatment. **Results** The NRS score (F = 23.573, P = 0.000) and HAMD score (F = 15.426, P = 0.000) before and after treatment were significantly different between the 2 groups. The NRS score and HAMD score in rTMS group were lower than those in control group at 1, 2, 3 and 4 weeks of treatment ($P \leq$ 0.01, for all). The differences in NRS score (F = 317.751, P = 0.000), HAMA score (F = 81.510, P = 0.000) and HAMD score (F = 32.773, P = 0.000) at different observation times were also statistically significant in the same treatment group. In rTMS group, NRS score and HAMD score at 1, 2, 3 and 4 weeks of treatment were lower than those before treatment and 3 days of treatment (P < 0.01, for all), and HAMA score at 1, 2 and 3 weeks of treatment were lower than those before treatment and 3 days of treatment (P = 0.000, for all). HAMA score at 4 weeks of treatment was lower than that before treatment (P = 0.007), at 1 week (P = 0.014) and 2 weeks (P = 0.001) of treatment. In control group, NRS score only at 4 weeks of treatment was lower than that before treatment (P = 0.000), HAMA score at 1, 2 and 3 weeks of treatment was lower than those before treatment (P < 0.05, for all), and HAMA score at 1 week of treatment was lower than that at 3 days of treatment (P = 0.002). Spearman correlation analysis showed that the degree of pain relief before and after treatment was positively correlated with the ease of anxiety (r_s = 0.442, P = 0.048) and depression (r_s = 0.705, P = 0.001). **Conclusions** High-frequency rTMS is a safe and effective treatment for NP with anxiety and/or depression. It can significantly ease anxiety and depression in patients while relieving pain.

【Key words】 Neuralgia; Transcranial magnetic stimulation; Mood; Rehabilitation

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神经病理性疼痛(NP)是临床常见的疼痛类型之一,发病机制不十分明确,病程从数月至数年不等[1-2],可导致焦虑和抑郁等情绪障碍[3-4],严重降低患者生活质量。重复经颅磁刺激(rTMS)作为一种安全无创、操作简便的神经调控与刺激技术,已广泛应用于临床镇痛治疗,且对情绪障碍具有显著改善作用[5]。目前,针对神经病理性疼痛伴焦虑或抑郁等情绪障碍的临床疗效评价研究较少,本研究基于神经心理学测验量表探讨重复经颅磁刺激对伴焦虑和(或)抑郁情绪的神经病理性疼痛患者临床症状的改善作用,对比分析治疗前后相关指标的变化,以为临床治疗神经病理性疼痛伴情绪障碍提供新的途径。

对象与方法

一、研究对象

1.纳入标准 (1)神经病理性疼痛的诊断符合2013年《神经病理性疼痛诊疗专家共识》[6]标准。(2)年龄18~60岁。(3)汉密尔顿焦虑量表14项(HAMA-14)[7]评分≥7分和(或)汉密尔顿抑郁量表17项(HAMD-17)[8]评分≥8分、疼痛数字评价量表(NRS)[9]评分≥4分、简易智能状态检查量表(MMSE)[10]评分>22分。(4)本研究经空军军医大学西京医院道德伦理委员会审核批准(审批号:HY20192049-F-2)。(5)所有患者或其家属对所行检查项目知情并签署知情同意书。

2.排除标准 (1)存在癫痫、颅内金属植入物、妊娠期等重复经颅磁刺激禁忌证。(2)合并颅内器质性病变或颅脑创伤。(3)正在服用纳洛酮等干扰重复经颅磁刺激镇痛作用的药物[11]。(4)合并痛风、外伤或手术后疼痛等其他原因引起的急性疼痛。(5)神经病理性疼痛发病前已患有焦虑和(或)抑郁等情绪障碍。(6)其他原因引起的焦虑和(或)抑郁等情绪障碍。

3.一般资料 选择2019年6月至2021年10月在我院康复医学科住院治疗的神经病理性疼痛伴情绪障碍患者共39例,男性28例,女性11例;年龄18~56岁,平均(34.49±9.13)岁;受教育程度高中及以下14例(35.90%),本科及以上25例(64.10%);病程0.50~3.50个月,平均为(1.71±0.90)个月;已婚33例(84.62%),未婚6例(15.38%)。既往合并高血压6例(15.38%)、糖尿病1例(2.56%)、高脂血症5例(12.82%),吸烟11例(28.21%)、饮酒20例(51.28%),镇痛药应用史31例(79.49%)。其中,腰髓损伤17例(43.59%)、胸髓损伤10例(25.64%)、颈髓损伤9例(23.08%)、马尾损伤3例(7.69%)。入院时日常生活活动能力量表(ADL)评分0~100分,中位评分为27.60(5.50,44.00)分;美国脊髓损伤协会(ASIA)分级A级21例(53.85%),B级9例(23.08%),C级7例(17.95%),D级2例(5.13%);脊

髓损伤独立性评估(SCIM)评分7~87分,中位评分为31.80(14.00,48.00)分。采用随机数字表法随机分为常规治疗并假刺激组(对照组,19例)和常规治疗辅助高频重复经颅磁刺激组(rTMS组,20例),两组一般资料比较,差异无统计学意义(均$P>0.05$,表1),均衡可比。

二、研究方法

1.常规治疗 所有患者入院后均予以普瑞巴林镇痛治疗,根据疼痛程度服用剂量为75~150 mg/次(2次/d)。同时辅助综合康复治疗,根据患者运动障碍程度及并发症情况,分别施以肌力训练、坐位训练、转移训练、步行训练、轮椅训练、日常生活活动能力等康复训练,并辅助电刺激、针灸、蜡疗等物理治疗;1次/d,每周5 d,连续治疗4周。

2.重复经颅磁刺激 (1)rTMS组:常规治疗同时增加重复经颅磁刺激治疗,采用CCY-1型磁场刺激仪(武汉依瑞德公司),"8"字线圈,最大磁场强度6 T。患者于安静无噪音环境下平躺在治疗床上,全身放松,头部保持不动,以疼痛对侧初级运动皮质(M1)为靶点,测定静息运动阈值(RMT),微调刺激线圈角度,选择运动诱发电位(MEP)稳定点为最佳刺激靶点;治疗时将线圈中心置于疼痛对侧大脑皮质M1区并与头皮相切,刺激频率为10 Hz,场强为80%静息运动阈值,每个序列刺激时间为1 s,序列间隔时间3 s,120个序列/d(1200次脉冲/d)。(2)对照组:在常规治疗的基础上,将磁刺激线圈以90°垂直于头皮的方式进行假性刺激[12]。两组患者均治疗1次/d,每周5 d,连续治疗4周。

3.疗效与安全性评价 于治疗前及治疗3 d和1、2、3、4周时进行疗效评价。(1)NRS量表[9]:评价镇痛治疗效果,总评分10分,0分为无疼痛,1~3分为轻度疼痛、4~6分为中度疼痛、7~10分为重度疼痛。(2)HAMA-14量表[7]:评价焦虑症状,评分<7分定义为无焦虑、7~13分为可能焦虑、14~20分为确定焦虑、21~28分为明显焦虑、≥29分为严重焦虑。(3)HAMD-17量表[8]:评价抑郁症状,评分<8分为无抑郁、8~17分为轻度抑郁、18~23分为中度抑郁、≥24分为重度抑郁。(4)安全性:监测重复经颅磁刺激治疗过程中发生的不良事件,如头痛、头晕、恶心、呕吐等,评价治疗安全性。

4.统计分析方法 采用SPSS 19.0统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用Mann-Whitney U检验或Fisher确切概率法。正态性检验采用Shapiro-Wilk检验,呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,采用重复测量的方差分析,两两比行LSD-t检验;呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示,采用Mann-Whitney U检验。重复经颅磁刺激治疗前后疼痛缓解值与情绪改善

表1 rTMS组与对照组患者一般资料的比较

Table 1. Comparison of general data between rTMS group and control group

观察指标	对照组(n=20)	rTMS组(n=19)	统计量值	P值
性别(例)			—	0.301
男性	16/20	12/19		
女性	4/20	7/19		
年龄($\bar{x}\pm s$,岁)	31.90±6.75	36.90±10.61	1.875	0.069
病程($\bar{x}\pm s$,月)	1.65±0.83	1.95± 0.99	1.028	0.311
受教育程度(例)			—	1.000
高中及以下	7/20	7/19		
大学及以上	13/20	12/19		
婚姻(例)			—	0.661
未婚	4/20	2/19		
已婚	16/20	17/19		
高血压(例)	3/20	3/19	—	1.000
糖尿病(例)	1/20	0/19	—	1.000
高脂血症(例)	3/20	2/19	—	1.000
吸烟(例)	5/20	6/19	—	0.731
饮酒(例)	10/20	10/19	—	1.000
损伤部位(例)			0.500	0.771
颈髓损伤	5/20	4/19		
胸髓损伤	6/20	4/19		
腰髓损伤	8/20	9/19		
马尾损伤	1/20	2/19		
ADL[$M(P_{25},P_{75})$,评分]	28.34 (9.50,42.50)	26.96 (5.00,46.50)	0.283	0.778
ASIA分级(例)			—	0.163
A级	9/20	12/19		
B级	7/20	2/19		
C级	4/20	3/19		
D级	0/20	2/19		
SCIM[$M(P_{25},P_{75})$,评分]	31.18 (11.25,48.00)	32.41 (17.00,47.25)	0.304	0.762
镇痛药应用史(例)	15/20	16/19	—	0.695

—, Fisher's exact probability, Fisher确切概率法。Two-independent-sample t test for comparison of age and duration, Mann-Whitney U test for comparison of sites of injury, ADL and SCIM,年龄和病程的比较采用两独立样本的t检验;损伤部位、ADL和SCIM的比较采用Mann-Whitney U检验。rTMS, repetitive transcranial magnetic stimulation,重复经颅磁刺激;ADL, Activity of Daily Living Scale,日常生活活动能力量表;ASIA, American Spinal Injury Association,美国脊髓损伤协会;SCIM, Spinal Cord Independence Measure,脊髓损伤独立性评估

表2 rTMS组与对照组患者治疗前后NRS评分的比较($\bar{x} \pm s$,评分)

Table 2. Comparison of NRS score between rTMS group and control group before and after treatment ($\bar{x} \pm s$, score)

组别	例数	治疗前(1)	治疗3 d(2)	治疗1周(3)	治疗2周(4)	治疗3周(5)	治疗4周(6)
对照组	20	5.80±1.28	4.90±1.33	4.50±1.15	4.80±1.58	4.70±1.13	4.40±0.94
rTMS组	19	5.53±1.02	4.74±0.93	3.16±0.96	2.84±0.90	2.16±0.60	2.05±0.85

rTMS,repetitive transcranial magnetic stimulation,重复经颅磁刺激

表3 rTMS组与对照组患者治疗前后NRS评分的重复测量设计的方差分析表

Table 3. ANOVA of repeated measurement design analysis of NRS score between rTMS group and control group before and after treatment

变异来源	*SS*	df	*MS*	*F*值	*P*值
处理因素	117.911	1	117.911	23.573	0.000
测量时间	144.275	1	144.275	317.751	0.000
处理×测量时间	43.091	1	43.091	94.904	0.000
组间误差	16.800	37	0.454		
组内误差	185.072	37	5.002		

表4 不同处理组同一观察时间点NRS评分的两两比较

Table 4. Pairwise comparison of NRS score in different treatment groups at the same observation time

组间两两比	*t*值	*P*值
治疗前	0.784	1.000
治疗3 d	0.468	1.000
治疗1周	3.846	0.010
治疗2周	5.611	0.000
治疗3周	7.285	0.000
治疗4周	6.727	0.000

表5 同一处理组不同观察时间点NRS评分的两两比较

Table 5. Pairwise comparison of NRS score at different observation times in the same treatment group

组内两两比	对照组		rTMS组		组内两两比	对照组		rTMS组	
	*t*值	*P*值	*t*值	*P*值		*t*值	*P*值	*t*值	*P*值
(1):(2)	2.613	0.471	2.234	0.830	(2):(6)	1.452	1.000	7.596	0.000
(1):(3)	3.774	0.157	6.702	0.000	(3):(4)	0.871	1.000	0.894	1.000
(1):(4)	2.903	0.236	7.596	0.000	(3):(5)	0.581	1.000	2.830	0.286
(1):(5)	3.194	0.101	9.532	0.000	(3):(6)	0.290	1.000	3.128	0.124
(1):(6)	4.065	0.004	9.830	0.000	(4):(5)	0.290	1.000	1.936	0.975
(2):(3)	1.161	1.000	4.468	0.001	(4):(6)	1.161	1.000	2.234	0.830
(2):(4)	0.290	1.000	5.362	0.000	(5):(6)	0.871	1.000	0.298	1.000
(2):(5)	0.581	1.000	7.298	0.000					

rTMS,repetitive transcranial magnetic stimulation,重复经颅磁刺激

值的相关性采用Spearman秩相关分析。以$P \leqslant 0.05$为差异具有统计学意义。

结　果

rTMS组与对照组患者治疗前后NRS评分差异具有统计学意义($P = 0.000$),同一处理组不同观察时间点NRS评分差异亦具有统计学意义($P = 0.000$;表2,3)。其中,rTMS组治疗1、2、3和4周时NRS评分不仅低于对照组(均$P \leqslant 0.01$,表4),同时低于治疗前和治疗3 d时(均$P < 0.01$);对照组仅治疗4周时NRS评分低于治疗前($P = 0.000$,表5)。

rTMS组与对照组治疗前后HAMD评分差异有统计学意义($P = 0.000$),且同一处理组不同观察时间点HAMA评分和HAMD评分差异亦有统计学意义(均$P = 0.000$;表6,7)。其中,rTMS组治疗1、2、3和4周时HAMD评分低于对照组(均$P < 0.01$,表8),且低于治疗前和治疗3 d时(均$P < 0.01$);治疗1、2和3周时HAMA评分低于治疗前和治疗3 d时(均$P = 0.000$),治疗4周时评分低于治疗前($P = 0.007$)和治疗1周($P = 0.014$)、2周($P = 0.001$)时,对照组治疗1、2和3周时HAMA评分均低于治疗前(均$P < 0.05$),治疗1周时评分HAMD低于治疗3 d时($P = 0.002$,表9)。

为进一步明确重复经颅磁刺激镇痛效果与情绪状态改善的关系,将rTMS组治疗前后疼痛缓解值(NRS评分降低值)与情绪改善值(HAMA和HAMD

表6 rTMS组与对照组患者治疗前后HAMA和HAMD评分的比较($\bar{x} \pm s$,评分)

Table 6. Comparison of HAMA score and HAMD score between rTMS group and control group before and after treatment ($\bar{x} \pm s$, score)

组别	例数	治疗前(1)	治疗3 d(2)	治疗1周(3)	治疗2周(4)	治疗3周(5)	治疗4周(6)
HAMA							
对照组	20	8.70±1.72	7.70±1.72	6.30±2.52	6.80±1.99	6.50±2.06	7.10±1.74
rTMS组	19	8.89±1.15	8.53±1.50	4.58±1.64	4.21±1.51	5.00±1.33	6.68±1.25
HAMD							
对照组	20	8.70±1.66	8.20±1.51	7.40±1.85	7.20±1.82	7.60±2.30	8.50±1.32
rTMS组	19	8.42±1.61	8.74±1.56	5.16±1.46	4.32±1.34	5.05±1.27	6.16±1.80

HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表; rTMS, repetitive transcranial magnetic stimulation, 重复经颅磁刺激

表7 rTMS组与对照组患者治疗前后HAMA和HAMD评分的重复测量设计的方差分析表

Table 7. ANOVA of repeated measurement design analysis of HAMA score and HAMD score between rTMS group and control group before and after treatment

变异来源	*SS*	df	*MS*	*F*值	*P*值	变异来源	*SS*	df	*MS*	*F*值	*P*值
HAMA						HAMD					
处理因素	44.000	1	44.000	3.784	0.059	处理因素	154.625	1	154.625	15.426	0.000
测量时间	152.502	1	152.502	81.510	0.000	测量时间	95.625	1	95.625	32.773	0.000
处理×测量时间	16.538	1	16.538	8.839	0.005	处理×测量时间	56.856	1	56.856	19.486	0.000
组间误差	430.265	37	11.629			组间误差	370.888	37	10.024		
组内误差	69.226	37	1.871			组内误差	107.959	37	2.918		

HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表

表8 不同处理组同一观察时间点HAMD评分的两两比较

Table 8. Pairwise comparison of HAMD score in different treatment groups at the same observation time

组间两两比	*t*值	*P*值	组间两两比	*t*值	*P*值
治疗前	0.527	1.000	治疗2周	5.451	0.000
治疗3 d	1.015	1.000	治疗3周	4.814	0.000
治疗1周	4.237	0.002	治疗4周	4.426	0.001

评分降低值)进行相关性分析,经Spearman秩相关分析显示,rTMS组治疗前后疼痛缓解值与抑郁状态改善值(r_s=0.705, P=0.001)和焦虑状态改善值(r_s=0.442, P=0.048)均呈正相关。

两组患者治疗期间均未出现严重不良事件,轻度反应仅表现为刺激部位胀痛(rTMS组1例)或头晕(rTMS组和对照组各1例),休息后缓解。两组患者不良反应发生率差异无统计学意义[5%(1/20)对10.53%(2/19); Fisher确切概率法: P=0.605]。

讨 论

国际疼痛学会将神经病理性疼痛定义为因躯体感觉系统损害或疾病导致的疼痛,全球患病率为3.3%~8.3%[6]。神经病理性疼痛的发病机制十分复杂,主要包括中枢及外周敏化、下行抑制系统失衡、电压门控钠离子和钙离子通道改变,以及神经可塑性改变等[13-14]。糖尿病、带状疱疹、脊髓损伤、脑卒中、多发性硬化、肿瘤等疾病均可引起神经病理性疼痛,主要以自发性疼痛、异常性疼痛、痛觉过敏或感觉异常为主要特征[15],也可出现失眠、体重增加以及情绪障碍等[16-17]。神经病理性疼痛与抑郁障碍之间存在显著的神经生物学关联,一方面神经病理性疼痛患者因长期慢性疼痛及对预后的担忧,出现忧虑和恐惧,导致睡眠质量下降,甚至出现焦虑和抑郁等情绪障碍[18],有研究显示,其情绪障碍发病率可高达47%[19];另一方面,神经病理性疼痛患者处于焦虑、抑郁等情绪障碍状态时,内啡肽和阿片受体等内源性镇痛物质减少,P物质、5-羟色胺(5-HT)和去甲肾上腺素等致痛物质,以及胆囊收缩素等抗镇痛物质表达水平升高[20-22],从而进一步加重患者疼痛不良体验,导致预后不良。

目前临床上常以钙通道阻滞药和阿片类药物等进行镇痛治疗,但由于神经病理性疼痛的发病机

表9 同一处理组不同观察时间点HAMA评分和HAMD评分的两两比较

Table 9. Pairwise comparison of HAMA score and HAMD score in the same treatment group at different observation times

组内两两比	HAMA		HAMD		组内两两比	HAMA		HAMD	
	*t*值	*P*值	*t*值	*P*值		*t*值	*P*值	*t*值	*P*值
对照组					rTMS组				
(1):(2)	1.833	0.991	0.957	1.000	(1):(2)	0.658	1.000	0.589	1.000
(1):(3)	4.398	0.001	2.489	0.594	(1):(3)	7.709	0.000	6.089	0.000
(1):(4)	3.482	0.039	2.872	0.256	(1):(4)	8.367	0.000	7.661	0.000
(1):(5)	4.032	0.005	2.106	0.913	(1):(5)	6.957	0.000	6.286	0.000
(1):(6)	2.932	0.218	0.383	1.000	(1):(6)	3.948	0.007	4.223	0.002
(2):(3)	2.566	0.517	4.223	0.002	(2):(3)	7.051	0.000	6.679	0.000
(2):(4)	1.649	0.999	1.532	1.000	(2):(4)	7.709	0.000	8.250	0.000
(2):(5)	2.199	0.856	1.915	0.979	(2):(5)	6.299	0.000	6.875	0.000
(2):(6)	1.100	1.000	1.149	1.000	(2):(6)	3.290	0.074	4.813	0.000
(3):(4)	0.916	1.000	0.383	1.000	(3):(4)	0.658	1.000	1.571	1.000
(3):(5)	0.367	1.000	0.383	1.000	(3):(5)	0.752	1.000	0.196	1.000
(3):(6)	1.466	1.000	2.106	0.913	(3):(6)	3.760	0.014	1.866	0.987
(4):(5)	0.550	1.000	0.766	1.000	(4):(5)	1.410	1.000	1.375	1.000
(4):(6)	0.550	1.000	2.489	0.594	(4):(6)	4.419	0.001	3.438	0.045
(5):(6)	1.100	1.000	1.723	0.997	(5):(6)	3.008	0.176	2.063	0.934

HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表; rTMS, repetitive transcranial magnetic stimulation, 重复经颅磁刺激

制尚不十分明确,药物治疗效果有限,只能降低约20%的疼痛程度,且存在耐药性和依赖性等不良反应[23];运动皮质电刺激和神经阻滞等有创性治疗不仅费用昂贵,且具有手术创伤和感染的风险[24]。重复经颅磁刺激作为一种新兴的神经刺激技术,因其安全无创和操作简便等特点广泛应用于临床,该技术基于电磁感应原理,利用刺激线圈中强大瞬变的电流产生的磁场穿透颅骨并作用于M1区或背外侧前额皮质(DPLFC)等疼痛调节相关脑区,从而调节脑组织代谢和神经电活动[25-27]。国际临床神经生理学联盟(IFCN)欧洲分会制定的《重复经颅磁刺激治疗循证指南》[5]将重复经颅磁刺激治疗分为3个证据等级,A级证据为治疗方案有确定疗效(definite efficacy),B级证据为治疗方案很可能有疗效(probable efficacy),C级证据为治疗方案或许有效(possible efficacy),并指出高频(≥5 Hz)重复经颅磁刺激作用于神经病理性疼痛患者疼痛对侧M1区为A级证据,即具有确定的镇痛疗效。此外,重复经颅磁刺激在情绪调节中也显示出良好的疗效,Li等[28]的一项单中心双盲试验显示,采用高频(20 Hz)重复经颅磁刺激刺激M1区可在缓解患者疼痛症状的同时,显著降低其抑郁评分(P = 0.009)和焦虑评分(P = 0.013)。Gayduk等[29]通过对22篇相关研究临床参数的回顾分析发现,重复经颅磁刺激治疗神经病理性疼痛伴抑郁患者,以"8"字线圈对疼痛对侧M1区进行10~20 Hz的高频刺激最为有效。Bonifácio等[30]认为,采用高频(10 Hz)重复经颅磁刺激刺激臂丛神经损伤的神经病理性疼痛患者疼痛对侧M1区,在缓解持续性疼痛(P < 0.001)和阵发性疼痛(P = 0.002)以及改善焦虑状态(P = 0.005)等方面具有较好的治疗作用。一项纳入18项临床研究共643例神经病理性疼痛患者的Meta分析显示,采用高频(10 Hz)重复经颅磁刺激刺激疼痛对侧M1区后,疼痛、抑郁和焦虑症状显著减轻,其疗效可持续至最后一次治疗后2周,且无严重不良事件[31]。

重复经颅磁刺激不仅可以靶向调控M1区、初级感觉皮质(S1)、背外侧前额皮质等脑区兴奋性,还可以促进神经递质释放、增强突触可塑性,上调脑源性神经营养因子(*BDNF*)基因表达[32-33]。国际神经调节学会-北美神经调节医学会(INS-NANS)制定的《重复经颅磁刺激治疗疼痛、头痛与抑郁共病专家共识》[34]也指出,重复经颅磁刺激对脑神经的调控可能是缓解抑郁情绪、实现神经病理性疼痛与情绪障碍共病治疗的新方案。值得注意的是,临床

上约有1/3的神经病理性疼痛患者因忽视疼痛诱发的情绪障碍，导致镇痛疗效欠佳[34-35]。为优化临床重复经颅磁刺激治疗方案，本研究在常规治疗基础上，对伴焦虑和(或)抑郁的神经病理性疼痛患者予以高频(10 Hz)重复经颅磁刺激，并进行基于神经心理学测验量表的镇痛效果和情绪改善评估，结果显示，rTMS组患者治疗后NRS评分低于对照组，表明在常规治疗基础上联合重复经颅磁刺激镇痛效果显著；此外，rTMS组治疗后患者HAMA评分和HAMD评分均低于治疗前，进一步的相关分析结果显示，rTMS组患者疼痛缓解值与情绪改善值呈正相关关系，与既往研究结果相一致[36-37]。对大鼠坐骨神经慢性压迫性损伤(CCI)模型的研究显示，脂肪酸酰胺水解酶(FAAH)外周抑制剂URB937和全身抑制剂URB597均可通过抑制神经元过度兴奋而发挥镇痛作用；而URB597尚可通过调节大脑皮质和边缘系统神经可塑性以缓解慢性压迫性损伤诱导的抑郁样行为[38]，该项研究发现不同脂肪酸酰胺水解酶抑制剂镇痛与抗抑郁作用的机制不同，表明虽然神经病理性疼痛存在与情绪障碍共病的情况，但缓解疼痛和改善情绪障碍的神经回路有所不同。因此，本研究所得结果仍需进一步开展机制学探究，以明确重复经颅磁刺激对伴焦虑和(或)抑郁的神经病理性疼痛患者疼痛和情绪改善的具体作用机制，指导临床实施个体化治疗方案。

本研究为单中心研究且样本量较小，未比较单独镇痛治疗与镇痛-抗抑郁联合治疗的差异，且观察指标多为主观量表评分，存在一定主观偏倚，尚待扩大样本量，设立更详细的分组，并纳入更多观察指标进一步探讨与总结，以为伴抑郁和(或)焦虑情绪的神经病理性疼痛患者提供最佳治疗方案。

综上所述，神经病理性疼痛发病机制复杂，本研究采用高频重复经颅磁刺激治疗伴焦虑和(或)抑郁的神经病理性疼痛患者，发现该项技术可在明显缓解疼痛症状的同时显著改善焦虑和抑郁情绪，为进一步优化临床重复经颅磁刺激治疗方案提供理论依据。

利益冲突 无

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