

doi: 10.13241/j.cnki.pmb.2018.20.025

经颅磁刺激联合丙戊酸钠注射液治疗癫痫持续状态的效果分析*

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摘要 目的:探讨经颅磁刺激(transcranial magnetic stimulate, TMS)联合丙戊酸钠注射液治疗癫痫持续状态的效果。**方法:**选择 2014 年 8 月到 2017 年 8 月在我院诊治的癫痫持续状态患者 79 例,根据治疗方法的不同分为观察组 40 例与对照组 39 例。对照组给予丙戊酸钠注射液治疗,观察组在对照组治疗的基础上给予经颅磁刺激治疗,两组均治疗 1 个月,比较其临床总有效率、治疗期间不良反应的发生情况及治疗前后低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)、总胆固醇(TC)、甘油三酯(TG)水平、行为能力评分、被动肌动力评分及主动肌动力评分的变化。**结果:**观察组与对照组总有效率分别为 97.5%和 84.6%,观察组显著高于对照组($P<0.05$)。治疗期间,观察组食欲下降、恶心呕吐、嗜睡、头痛等不良反应发生率为 10.0%,对照组为 12.8%,两组对比无显著差异($P>0.05$)。治疗后,观察组 TG、TC 与 LDL-C 水平显著低于对照组($P<0.05$),两组 HDL-C 含量对比无显著差异($P>0.05$)。治疗后,观察组的行为能力评分、被动肌动力评分、主动肌动力评分都高于对照组($P<0.05$)。**结论:**经颅磁刺激联合丙戊酸钠注射液治疗癫痫持续状态能显著提高治疗效果,改善患者的神经行为功能,且不会影响患者的血脂水平与增加不良反应。

关键词:经颅磁刺激;丙戊酸钠注射液;癫痫持续状态;血脂水平;神经行为功能

中图分类号:R742.1;Q64 **文献标识码:**A **文章编号:**1673-6273(2018)20-3913-04

Effects of Transcranial Magnetic Stimulation Combined with Sodium Valproate Injection in the Treatment of Status Epilepticus*

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ABSTRACT Objective: To explore the effects of transcranial magnetic stimulation combined with valproate injection in the treatment of status epilepticus. **Methods:** We selected 79 patients with status epilepticus who were diagnosed and treated in our hospital from August 2014 to August 2017. According to the different treatment methods, 40 patients were divided into observation group and 39 control groups. The control group was treated with sodium valproate injection, while the observation group was treated with transcranial magnetic stimulation on the basis of the control group. The two groups were treated for 1 months. Comparing the clinical total effective rate, occurrence of adverse reactions during treatment, and before and after treatment [All initial English abbreviations in the thesis must be supplemented with full English names] Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG) levels, behavioral ability scores, passive muscle force scores, and active muscle force scores. **Results:** The total effective rate of the observation group and the control group were 97.5% and 84.6% respectively, and the observation group was significantly higher than that of the control group ($P<0.05$). During the treatment, the incidence of adverse reactions such as headache, drowsiness, nausea and decreased appetite in the observation group was 10%, while that in the control group was 12.8%. There was no significant difference compared between the two groups ($P>0.05$). After treatment, the levels of TG, TC and LDL-C in the observation group were significantly lower than those in the control group ($P<0.05$). There was no significant difference in the HDL-C levels between the two groups ($P>0.05$). After treatment, the scores of the active muscle tension, the passive muscle tension and the behavioral ability of the observation group were significantly higher than those of the control group ($P<0.05$). **Conclusion:** Transcranial magnetic stimulation combined with sodium valproate injection in the treatment of status epilepticus can significantly improve the therapeutic effect, improve the patient's neurobehavioral function, and will not affect the patient's blood lipid levels and increase adverse reactions.

Key words: Transcranial magnetic stimulation; Sodium valproate injection; Status epilepticus; Blood lipid level; Neurobehavioral function

Chinese Library Classification(CLC): R742.1; Q64 **Document code:** A

Article ID: 1673-6273(2018)20-3913-04

* 基金项目:陕西省重点研发计划项目(2017SF-264)

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(收稿日期:2018-03-04 接受日期:2018-04-03)

前言

癫痫具有发病率高、致残率高等特点,反复的癫痫发作可引起脑损伤^[3,4]。现代研究表明癫痫持续状态发生的病机是致神经元网的同步高度化异常放电导致大脑皮质异常兴奋状态所致^[5,6]。癫痫的治疗方法较多,以药物治疗在临床上比较常见^[7,8]。丙戊酸钠注射液是一种广谱抗癫痫药物,对治疗全面性发作癫痫与局灶性发作癫痫均有效,且剂量增加未发现加重癫痫症状的现象^[9,10]。但丙戊酸钠注射液在发挥抗癫痫作用的同时,也带来了一定的不良反应,严重情况下可产生致死性肝脏损害,还可导致体重增加、高脂血症等^[11]。

经颅磁刺激(transcranial magnetic stimulate, TMS)是上个世纪就已经建立的皮层刺激方法,具有无痛、无损伤、操作简便、安全可靠等优点。经颅磁刺激在临床上可兴奋运动皮层,可提高帕金森患者的反应能力及减少癫痫患者的发作频率等^[12-14],但是与药物联合治疗的报道还未多见。本研究主要探讨了

经颅磁刺激联合丙戊酸钠注射液治疗癫痫持续状态的效果,以期合理选择经颅磁刺激治疗提供参考。

1 材料与方法

1.1 一般资料

本研究为单中心、回顾性、随机抽样、单盲研究方法,研究时间为2014年8月到2017年8月,选择在我院诊治的癫痫持续状态患者79例,医院伦理委员会批准了此次研究,纳入标准:年龄18-60岁;符合癫痫持续状态的诊断标准;蒙特利尔认知评估量表(MoCA)评分<25分;患者在纳入前1年内至少有2次明确的癫痫发作;以往未服用过任何抗癫痫药物与进行经颅磁刺激治疗;治疗前血脂检测在正常范围内。排除标准:孕妇或哺乳期患者;颅内占位病变、恶性肿瘤、颅内出血病变患者;合并其他严重躯体疾病患者。根据治疗方法不同分为观察组(n=40)与对照组(n=39),两组发作频率、发作类型比较差异均无统计学意义($P>0.05$),具有可比性。见表1。

表1 两组患者一般资料对比

Table 1 Comparison of the general data between two groups

Groups	n	Gender (male/female)	Age (year)	Seizure frequency (secondary/month)	Type of attack (focal/comprehensive)	Course of disease (year)
Observation group	40	23/17	7.22± 1.22	3.02± 0.66	28/12	3.55± 0.34
Control group	39	20/19	7.29± 1.43	2.89± 0.61	28/11	3.40± 0.55
<i>P</i>		>0.05	>0.05	>0.05	>0.05	>0.05

1.2 治疗方法

对照组:给予丙戊酸钠治疗,丙戊酸钠(国药准字H20084540,沈阳新马药业有限公司)起始剂量为20-30 mg/kg·d,每日进行3次静脉滴注;当达到有效血药浓度并维持时以15 mg/kg 剂量缓慢静脉推注。

观察组:在对照组治疗的基础上给予经颅磁刺激治疗,选择英国Magstim公司的经颅磁刺激仪,使用环形线圈,直径12.5 cm。患者安静平卧,刺激部位在左前额叶背外侧,线圈放置与头皮平行,将其下颞置于固定支架上。刺激参数:频率1 Hz,刺激10 s,间隔5 s,重复100次,持续25 min,总共刺激1000次,1次/d。

两组都治疗观察1个月。

1.3 观察指标

1.3.1 疗效标准 以治疗前与治疗后1个月内的发作频率变化进行比较,分为控制、显效、有效、无效等四个级别。总有效率(%)=(控制+显效+有效)/组内例数×100%。

1.3.2 不良反应情况 记录两组在治疗期间的食欲下降、恶心

呕吐、嗜睡、头痛等不良反应的发生情况。

1.3.3 血脂测定 在治疗后抽取患者清晨空腹静脉血3-4 mL,3000 r/min 离心15-20 min,留取上层血清,测定低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)、总胆固醇(TC)、甘油三酯(TG),测定仪器为Japan日立公司7100型全自动生化分析仪。

1.3.4 神经行为评分 于治疗后测试被动肌张力、主动肌张力和行为能力评分,分数越高,代表神经行为能力越强。

1.4 统计学分析

采用统计学软件SPSS21.00,计量数据($\bar{x} \pm s$)与计数数据(%)的对比方法涉及到t检验、 χ^2 分析等,以 $P<0.05$ 代表差异具有统计学意义。

2 结果

2.1 两组总有效率的对比

观察组与对照组总有效率分别为97.5%和84.6%,观察组显著高于对照组($P<0.05$),见表2。

表2 两组患者的治疗总有效率对比(n)

Table 2 Comparison of the total efficacy of treatment between two groups (n)

Groups	n	Control	Excellent	Effective	Invalid	Total effective(%)
Observation group	40	26	10	3	1	97.5
Control group	39	9	16	8	6	84.6
<i>P</i>						<0.05

2.2 两组治疗期间不良反应的发生情况对比

反应发生率为 10.0%, 对照组为 12.8%, 两组对比差异无统计学意义($P>0.05$)。见表 3。

治疗期间, 观察组食欲下降、恶心呕吐、嗜睡、头痛等不良

表 3 两组治疗期间不良反应发生情况对比(n)

Table 3 Comparison of the incidence of adverse reactions between the two groups during treatment(n)

Groups	n	Headache	Drowsiness	Nausea	Loss of appetite	Total(%)
Observation group	40	1	1	1	1	10.0
Control group	39	1	2	0	2	12.8
<i>P</i>						<0.05

2.3 血脂检测结果对比

($P<0.05$), 两组 HDL-C 水平对比无显著差异($P>0.05$), 见表 4。

治疗后, 观察组 TG、TC 与 LDL-C 水平均显著低于对照组

表 4 两组治疗后血脂含量的对比(mmol/L, $\bar{x}\pm s$)

Table 4 Comparison of the serum lipids between two groups (mmol/L, $\bar{x}\pm s$)

Groups	n	TC	TG	HDL-C	LDL-C
Observation group	40	4.98 $\pm$ 0.55	1.13 $\pm$ 0.45	1.34 $\pm$ 0.35	2.67 $\pm$ 0.79
Control group	39	5.75 $\pm$ 0.41	2.81 $\pm$ 0.45	1.31 $\pm$ 0.42	3.94 $\pm$ 0.65
<i>P</i>		<0.05	<0.05	>0.05	<0.05

2.4 两组治疗后神经行为评分的对比

动力评分都高于对照组($P<0.05$), 见表 5。

治疗后, 观察组的行为能力评分、被动肌动力评分、主动肌

表 5 两组治疗后的神经行为评分对比(分, $\bar{x}\pm s$)

Table 5 Comparison of the neurobehavioral scores after treatment between two groups (score, $\bar{x}\pm s$)

Groups	n	Active muscle tone	Passive muscular tension	Behavioral skills
Observation group	42	12.98 $\pm$ 0.98	7.54 $\pm$ 0.65	7.61 $\pm$ 0.6
Control group	42	10.35 $\pm$ 0.67	7.02 $\pm$ 0.45	6.61 $\pm$ 0.78
<i>P</i>		<0.05	<0.05	<0.05

3 讨论

癫痫持续状态在临床上主要表现为口齿不清、流涎、面肌抽搐、喉头发声等, 具有多种发作类型, 存在认知损害及行为异常^[15]。多数癫痫持续状态患者可找到脑损伤病因, 病因不明者约占 25%^[16]。随着近年对癫痫的发病机制和抗癫痫药物作用机制的研究发展, 越来越多的抗癫痫药物被用于癫痫的治疗中^[17]。目前, 治疗癫痫的药物包括卡马西平、丙戊酸钠、苯巴比妥、苯妥英钠等。丙戊酸钠可改变患者激素水平, 抑制睾酮向雌二醇的转化; 也可与 GABA 的合成酶和降解酶产生反应, 增强 GABA 的活性, 从而发挥抗癫痫作用^[18]。

经颅磁刺激是一种神经电生理技术, 使神经细胞去极化并产生诱发电位, 诱发一定强度的感应电流, 在治疗抑郁症、精神分裂症、帕金森、肌张力障碍都取得了比较好的效果^[19]。经颅磁刺激也可诱导产生突触间的长时程抑制, 影响大脑神经皮质突触发生重塑, 逆转受损突触的功能, 减少癫痫发作间期、发作期的异常放电^[20]。丙戊酸钠是一种非镇静性抗惊厥药物, 能活化谷氨酸脱氢酶, 也能轻易透过血-脑脊液屏障, 从而起到抗惊厥作用^[21]。本研究显示经颅磁刺激治疗联合丙戊酸钠注射液治疗的癫痫持续状态患者总有效率显著高于单用丙戊酸钠注射液治疗。此外, 观察组治疗期间食欲下降、恶心呕吐、嗜睡、头痛

等不良反应发生率为 10.0%, 对照组为 12.8%, 表明经颅磁刺激的应用具有很好的安全性。相关研究也显示适量低频经颅磁刺激能抑制颞叶癫痫大鼠的细胞凋亡, 从而减轻癫痫所致的脑部损伤; 其也能通过减少神经元坏死, 发挥抗惊厥作用^[22,23]。

癫痫是一种反复发作的抽搐和 / 或痉挛的神经系统疾, 应尽早进行抗癫痫治疗。相对于一般人群, 癫痫患者的糖耐量明显升高, 会增高皮质兴奋性, 使发作频率增加^[24]。本研究显示观察组治疗后 TG、TC 与 LDL-C 显著低于对照组, 可能原因是经颅磁刺激具有频率依赖性, 可以降低大脑葡萄糖代谢率, 从而起到抗癫痫作用^[25]。

癫痫持续状态对患者的认知功能有比较大的损害^[26]。有研究表明即便癫痫发作得到完全控制, 神经与认知功能损害也往往难以恢复^[27,28]。为此对癫痫患者的治疗不仅要控制临床发作, 还要改善患者的认知功能。本研究结果显示观察组治疗后的行为能力评分、被动肌动力评分、主动肌动力评分都高于对照组, 可能与经颅磁刺激可以通过双向调节兴奋性及抑制性神经递质, 促进大脑相应区域的多巴胺释放, 使去甲肾上腺素的结合增多, 少痫样放电发生及发作次数有关^[29,31]。

总之, 经颅磁刺激联合丙戊酸钠注射液治疗癫痫持续状态能显著提高治疗效果, 改善患者的神经行为功能, 且不会影响患者的血脂水平与增加不良反应。

参 考 文 献(References)

- [1] Shiba T, Hamahata K, Yoshida A. Acute encephalopathy with biphasic seizures and late reduced diffusion in Kawasaki disease[J]. *Pediatr Int*, 2017, 59(12): 1276-1278
- [2] Cormier J, Maciel CB, Gilmore EJ. Ictal-Interictal Continuum: When to Worry About the Continuous Electroencephalography Pattern[J]. *Semin Respir Crit Care Med*, 2017, 38(6): 793-806
- [3] Rybka S, Obniska J, Rapacz A, et al. Synthesis, Physicochemical, and Anticonvulsant Properties of New N-Mannich Bases Derived from Pyrrolidine-2,5-dione and Its 3-Methyl Analog [J]. *Arch Pharm (Weinheim)*, 2014, 347(10): 768-776
- [4] Hammoud MZ, Milad MR. Symptom Changes in Posttraumatic Stress Disorder and Major Depressive Disorder After Transcranial Magnetic Stimulation: Mechanisms of Where and How in the Brain [J]. *Biol Psychiatry*, 2018, 83(3): 200-202
- [5] Luz-Santos C, Ribeiro Camatti J, Barbosa Paixão A, et al. Additive effect of tDCS combined with Peripheral Electrical Stimulation to an exercise program in pain control in knee osteoarthritis: study protocol for a randomized controlled trial[J]. *Trials*, 2017, 18(1): 609
- [6] Nucera A, Azarpazhooh MR, Cardinali L, et al. Inhibition of the primary motor cortex and the upgoing thumb sign [J]. *eNeurologicalSci*, 2017, 19(8): 31-33
- [7] Gaede G, Tiede M, Lorenz I, et al. Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue [J]. *Neurol Neuroimmunol Neuroinflamm*, 2017, 5(1): e423
- [8] Harvey DY, Podell J, Turkeltaub PE, et al. Functional Reorganization of Right Prefrontal Cortex Underlies Sustained Naming Improvements in Chronic Aphasia via Repetitive Transcranial Magnetic Stimulation[J]. *Cogn Behav Neurol*, 2017, 30(4): 133-144
- [9] Finisguerra A, Amoruso L, Makris S, et al. Dissociated Representations of Deceptive Intentions and Kinematic Adaptations in the Observer's Motor System[J]. *Cereb Cortex*, 2018, 28(1): 33-47
- [10] Thomas F, Bouaziz N, Amengual JL, et al. Unexpected Improvement of Hand Motor Function with a Left Temporoparietal Low-Frequency Repetitive Transcranial Magnetic Stimulation Regime Suppressing Auditory Hallucinations in a Brainstem Chronic Stroke Patient [J]. *Front Psychiatry*, 2017, 28(8): 262
- [11] Pardoe HR, Berg AT, Jackson GD. Sodium valproate use is associated with reduced parietal lobe thickness and brain volume[J]. *Neurology*, 2013, 80(20): 1895-1900
- [12] Wang HN, Wang XX, Zhang RG, et al. Clustered repetitive transcranial magnetic stimulation for the prevention of depressive relapse/recurrence: a randomized controlled trial [J]. *Transl Psychiatry*, 2017, 7(12): 1292
- [13] Ulrich M, Lorenz S, Spitzer MW, et al. Theta-burst modulation of mid-ventrolateral prefrontal cortex affects salience coding in the human ventral tegmental area[J]. *Appetite*, 2017, 13(123): 91-100
- [14] Ferrari C, Oldrati V, Gallucci M, et al. The role of the cerebellum in explicit and incidental processing of facial emotional expressions: A study with transcranial magnetic stimulation [J]. *Neuroimage*, 2017, 12(169): 256-264
- [15] Jin JN, Wang X, Li Y, et al. The Effects of rTMS Combined with Motor Training on Functional Connectivity in Alpha Frequency Band [J]. *Front Behav Neurosci*, 2017, 29(11): 234
- [16] Nogueira AB, Nogueira AB, Veiga JCE, et al. Hypothesis on the Role of Cryptochromes in Inflammation and Subarachnoid Hemorrhage Outcome[J]. *Front Neurol*, 2017, 28(8): 637
- [17] Collins BW, Button DC. The effect of shoulder position on motor evoked and maximal muscle compound action potentials of the biceps brachii[J]. *Neurosci Lett*, 2017, 8(665): 206-211
- [18] Ghaleiha A, Haghighi M, Sharifmehr M, et al. Oral loading of sodium valproate compared to intravenous loading and oral maintenance in acutely manic bipolar patients [J]. *Neuropsychobiology*, 2014, 70(1): 29-35
- [19] Gersner R, Dhamne SC, Zangen A, et al. Bursts of high-frequency repetitive transcranial magnetic stimulation (rTMS), together with lorazepam, suppress seizures in a rat kainate status epilepticus model [J]. *Epilepsy Behav*, 2016, 9(62): 136-139
- [20] Schreiber JM, Pearl PL, Dustin I, et al. Biomarkers in a Taurine Trial for Succinic Semialdehyde Dehydrogenase Deficiency[J]. *JIMD Rep*, 2016, 9(30): 81-87
- [21] Wandschneider B, Thompson PJ, Vollmar C, et al. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data [J]. *Epilepsia*, 2012, 53(12): 2091-2098
- [22] Carrabba G, Bertani G, Cogiamanian F, et al. Role of Intraoperative Neurophysiologic Monitoring in the Resection of Thalamic Astrocytomas[J]. *World Neurosurg*, 2016, 10(94): 50-56
- [23] Carrette S, Boon P, Dekeyser C, et al. Repetitive transcranial magnetic stimulation for the treatment of refractory epilepsy [J]. *Expert Rev Neurother*, 2016, 16(9): 1093-110
- [24] Palanisamy A, Rajendran NN, Narmadha MP, et al. Association of apolipoprotein Eε4 allele with cognitive impairment in patients with epilepsy and interaction with phenytoin monotherapy [J]. *Epilepsy Behav*, 2013, 26(2): 165-169
- [25] Pereira LS, Müller VT, da Mota Gomes M, et al. Safety of repetitive transcranial magnetic stimulation in patients with epilepsy: A systematic review[J]. *Epilepsy Behav*, 2016, 57(Pt A): 167-176
- [26] Gryn SE, Teft WA, Kim RB. Profound reduction in the tamoxifen active metabolite endoxifen in a patient on phenytoin for epilepsy compared with a CYP2D6 genotype matched cohort [J]. *Pharmacogenet Genomics*, 2014, 24(7): 367-369
- [27] Dhamne SC, Ekstein D, Zhuo Z, et al. Acute seizure suppression by transcranial direct current stimulation in rats [J]. *Ann Clin Transl Neurol*, 2015, 2(8): 843-856
- [28] Kimiskidis VK, Valentin A, Kälviäinen R. Transcranial magnetic stimulation for the diagnosis and treatment of epilepsy [J]. *Curr Opin Neurol*, 2014, 27(2): 236-241
- [29] Liu A, Pang T, Herman S, et al. Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit[J]. *Seizure*, 2013, 22(10): 893-896
- [30] DeGiorgio AC, Desso TE, Lee L, et al. Ventricular tachycardia associated with lacosamide co-medication in drug-resistant epilepsy [J]. *Epilepsy Behav Case Rep*, 2012, 7(1): 26-28
- [31] Thordstein M. Navigated Transcranial Magnetic Stimulation (nTMS). Technology for more precise diagnosis and therapy of central nervous system dysfunctions[J]. *Lakartidningen*, 2013, 110(13-14): 678-681