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托吡酯联合拉莫三嗪对癫痫患者认知功能和生活质量的影响 *

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摘要 目的:探讨托吡酯联合拉莫三嗪对癫痫患者认知功能和生活质量的影响。**方法:**选择2016年1月到2018年2月我院诊治的癫痫患者60例进行回顾性分析,根据治疗方法不同分为两组,各30例,对照组给予托吡酯治疗,观察组在对照组治疗的基础上给予拉莫三嗪治疗。两组均治疗观察3个疗程,记录和比较其认知功能和生活质量变化情况以及不良反应发生情况。**结果:**治疗后,观察组的总有效率显著高于对照组(96.6% vs. 73.3%,*P*<0.05)。两组治疗期间的胃肠道反应、神经系统反应、精神症状、全身反应等不良反应情况对比差异无统计学意义(*P*>0.05)。两组治疗后的蒙特利尔认知评估量表(Montreal Cognitive Assessment,MoCA)评分均显著高于治疗前(*P*<0.05),且观察组显著高于对照组(*P*<0.05)。此外,观察组治疗后的生活满意度、生活打扰、积极影响、身体健康、心理应对等生活质量评分均显著高于对照组(*P*<0.05)。**结论:**托吡酯联合拉莫三嗪用于治疗癫痫患者能显著改善认知功能,提高患者生活质量与治疗效果,且安全性较高。

关键词:托吡酯;拉莫三嗪;癫痫;认知功能;生活质量

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Effects of Topiramate Combined with Lamotrigine on Cognitive Function and Quality of Life in Patients with Epilepsy*

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ABSTRACT Objective: To investigate the effects of topiramate combined with lamotrigine on cognitive function and quality of life in patients with epilepsy. **Methods:** Sixty patients with epilepsy who were treated in our hospital from January 2016 to February 2018 were retrospectively analyzed. According to different treatment methods, they are divided into two groups, 30 cases each. The control group were treated with topiramate, the observation group were given with lamotrigine on the basis of the control group. The two groups were treated for 3 courses, the changes in cognitive function, quality of life and the incidence of adverse reactions were recorded and compared. **Results:** After treatment, the total effective rate of the observation group was significantly higher than that of the control group (96.6% vs. 73.3%, *P*<0.05). There were no significant differences in adverse reactions of gastrointestinal reactions, nervous system reactions, psychotic symptoms and systemic reactions comapred betweeen the two gorups during the treatment(*P*>0.05). The MoCA scores of the two groups were significantly higher than those before treatment (*P*<0.05), and the observation group were significantly higher than the control group (*P*<0.05). In addition, the quality of life scores of life observation, life interruption, positive influence, physical health, and psychological coping were significantly higher in the observation group than in the control group (*P*<0.05). **Conclusion:** Topiramate combined with lamotrigine for the treatment patients with epilepsy can significantly improve cognitive function, improve patients' quality of life and treatment, and have higher safety.

Key words: Topiramate; Lamotrigine; Epilepsy; Cognitive function; Quality of life

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前言

癫痫是一种由多种病因引起的慢性脑部疾病,是最常见的神经系统疾病之一，约占世界人口的1%-4%，全世界超过5000万人都深受其害[1,2]。80%左右的癫痫患者起病年龄在20岁以前,癫痫对患者的生长发育、生活、学习等都会带来严重不良影响,部分病例会延续至成人期,给患者带来极大痛苦,严重影响患者和家庭的生活质量[3,4]。癫痫患者认知障碍被认为是认知功能正常到痴呆的过渡状态，在癫痫患者中患病率约为40%，不仅影响患者的生存质量，也是导致患者死亡的危险因素[5,6]。癫痫患者的身心状态比较虚弱,加上自身疾病知识缺乏,也会产生不同程度的心理负担,影响患者的生活质量[7,8]。

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目前，癫痫仍以药物治疗为主要手段，需长期用药甚至终身用药，常用的药物包括丙戊酸钠、卡马西平、苯妥英钠、奥卡西平、托吡酯、左乙拉西坦等，但上述药物在使用中均存在一定的不良反应，特别是抗癫痫药物所致的高同型半胱氨酸血症在临床上比较多见，可直接影响药物的应用及癫痫的治疗效果[9,10]。拉莫三嗪的化学名为 3，5- 二氨基 -6-(2，3- 二氯苯基)-as- 三吖嗪，可促进谷氨酸的释放，从而稳定神经细胞膜，抑制兴奋性电压依赖性钠通道，进而发挥抗癫痫的作用[11]。并且该药有吸收迅速、完全等特点，不良反应少于其它同类药品[12]。因此，本研究主要探讨了托吡酯联合拉莫三嗪对癫痫患者认知功能和生活质量的影响，以明确拉莫三嗪的辅助临床应用价值。

1 资料与方法

1.1 研究对象

选择在我院诊治的癫痫患者 60 例，研究时间段为 2016 年 1 月到 2018 年 2 月，纳入标准：年龄 12-40 岁；家长或监护人已签署知情同意书；临床资料完整；根据临床表现及视频脑电图检查确诊为癫痫；无特殊饮食史；均有良好的用药依从性；我院伦理委员会批准了此次研究。排除标准：肝脏肾脏功能检查明显异常者；临床资料缺乏者；对本研究使用药物过敏者；因个人原因要求退出者。根据治疗方法不同分为两组，且一般资料具有可比性。

表 1 两组一般资料对比

Table 1 Comparison of general data between the two groups

Groups	N	Course of disease (year)	Body mass index (kg/m^2)	Gender (male/female)	Age	Etiology (hereditary/metabolic/unexplained)
Observation group	30	6.20± 1.20	22.88± 2.47	45/35	21.10± 2.18	35/31/4
Control group	30	6.13± 1.82	22.10± 3.18	34/30	20.02± 1.99	31/28/4
t/x^2	-	0.244	0.561	0.140	0.188	0.027
P	-	0.687	0.378	0.708	0.713	0.987

1.2 治疗方法

对照组口服托吡酯 (西安杨森制药有限公司，国药准字 H20020555)治疗，剂量为 5-9 $mg·kg^{-1}/d$，分 2 次服用。观察组在对照组治疗的基础上给予拉莫三嗪治疗，口服拉莫三嗪(国药准字 H20143194，湖南三金制药有限责任公司)，剂量为 150-250 mg/ 次，1 次 /d。4 周为一个疗程，两组均治疗 3 个疗程。

1.3 观察指标

(1)疗效标准：控制：癫痫发作完全控制，治疗期间无复发。显效：癫痫发作频率减少 >75 %，治疗期间无复发。有效：发作频率减少 50 %-75 %，治疗期间无复发。无效：未达到上述标准甚或加重。(2)记录两组在治疗期间出现的不良反应情况。(3)分别于治疗前后采用蒙特利尔认知评估量表 (Montreal Cognitive Assessment，MoCA)对两组患者进行评定，包括注意与集中、执行功能、记忆以及语言等在内的 8 个认知领域，检查项目共 11 项，满分为 30 分，分数越高，认知功能越正常。(4)治疗后采用生活质量量表(Quality of life, QOL)完成对所有患者的评定，包括生活满意度、生活打扰、积极影响、身体健康等维度，分数越高，生活质量越好。

1.4 统计学分析

采用 SPSS 20.00 进行数据分析，计量数据以($\bar{x}\pm s$)表示，行 t 检验；计数数据以%表示，行 x^2 检验，$P<0.05$ 表示具有统计学差异。

2 结果

2.1 两组治疗后总有效率的比较

治疗后，观察组总有效率显著高于对照组($P<0.05$)。见表2。

表 2 两组总有效率对比[例(%)]

Table 2 Comparison of the total effective rate between the two groups[n(%)]

Groups	N	Control	Significant effect	Effective	Invalid	The total efficiency
Observation group	30	11(36.67)	12(40.00)	6(20.00)	1(3.33)	29(96.6%)
Control group	30	5(16.67)	10(33.33)	7(23.33)	8(26.67)	22(73.3%)
x^2						6.405
P						0.026

2.2 两组不良反应的发生情况比较

观察组胃肠道反应、神经系统反应、精神症状、全身反应等不良反应的发生情况对比差异无统计学意义($P>0.05$)。表 3。

2.3 两组治疗前后认知功能评分的比较

两组治疗后的 MoCA 评分均显著高于治疗前，且观察组显著高于对照组($P<0.05$)。见表 4。

2.4 两组治疗后生活质量评分的比较

治疗后，观察组的生活满意度、生活打扰、积极影响、身体健康、心理应对等生活质量评分均显著高于对照组($P<0.05$)。见表 5。

表 3 两组治疗期间不良反应发生情况的对比[例(%)]

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

Group	N	Gastrointestinal reaction	Nervous system response	Mental symptoms	Systemic response
Observation group	30	0(0.00)	1(3.33)	0(0.00)	1(3.33)
Control group	30	2(6.67)	3(10.00)	3(10.00)	4(13.33)
x^2		2.069	1.071	3.158	1.964
P		0.492	0.612	0.237	0.353

表 4 两组治疗前后 MoCA 评分变化评分对比($\bar{x}\pm s$,分)

Table 4 Comparison of the changes in MoCA scores before and after treatment in both groups ($\bar{x}\pm s$, score)

Groups	N	Before treatment	After treatment	t	*P*
Observation group	30	20.47± 2.18	28.33± 1.72	-15.504	＜0.001
Control group	30	20.87± 1.73	25.63± 2.11	-9.555	＜0.001
t				-0.787	5.433
P				0.434	＜0.001

表 5 两组治后生活质量评分对比($\bar{x}\pm s$,分)

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

Groups	N	Healthy body	Life satisfaction	Psychological response	Positive influence	Disturbing life
Observation group	30	20.63± 4.31	43.36± 5.10	9.34± 1.34	15.33± 3.94	43.34± 8.15
Control group	30	16.94± 5.34	40.21± 6.43	8.43± 1.42	12.81± 4.13	38.13± 7.21
t		2.945	2.102	2.553	2.418	2.622
P		0.005	0.040	0.013	0.019	0.011

3 讨论

癫痫在任何年龄、地区和种族的人群中都有发病，是一种世界性常见病、多发病，但以儿童和青少年发病率较高[13]。虽然以托吡酯为代表的抗癫痫药物在临床上的应用有效率高，不良反应多属轻微、可逆。但个体对药物的耐受程度不同，且长期服用对于患者的依从性比较高，且会对患者身心造成新的损伤[14-17]。

拉莫三嗪是可产生一种电压依从性阻滞持续的反复放电，可发挥抗癫痫作用[18]。本研究表明拉莫三嗪的联合应用可提高治疗效果，且不会增加不良反应的发生。当前研究也显示拉莫三嗪可阻断神经元持续去极化导致的反复电位发放，阻断钠通道，可协调患者的细微视觉运动的协调和眼球运动，改善患者的预后[19]。

认知障碍是介于健康人与痴呆之间的临床过渡状态，约40%的癫痫患者在病程晚期会发生痴呆。MoCA 是一种快速检测认知障碍的工具，具有较好的敏感性即特异性；该量表通过早期认知功能损伤常涉及的 7 个项目 10 道题目测试评价受试者的认知功能的损伤情况，也是有效发现癫痫患者早期认知功能损伤的测试手段[20,21]。本研究显示两组治疗后的 MoCA 评分都显著高于治疗前，观察组显著高于对照组，表明拉莫三嗪的联合应用可促进患者的认知功能改善。也有研究显示拉莫三嗪可阻断机体内 DNA 甲基化反应、氨基硫醇氧化还原等异常反应，促进蛋白质的生物代谢合成以及髓鞘形成，可减少双相情感障碍患者的焦虑和可卡因使用，也可用于治疗创伤后应激障碍、难治性精神分裂症等[22,23]。

癫痫患者有些同时伴有智力障碍，而高同型半胱氨酸(Hcy)血症在早期可无症状，癫痫发作加重可能被认为是药物控制效果欠佳，往往增加剂量或联合用药而使症状进一步加重，不利于患者预后生活质量的改善[24,25]。特别是多药治疗有可能达不到预期目的，有时甚至导致发作增加和不良反应增大[26]。本研究中观察组治疗后的生活质量评分各维度均显著高于对照组，表明联合用药能提高患者的生活质量。相关研究显示癫痫患者辅助给予维生素，可降低癫痫发作程度，改善认知能力[27,28]。不过癫痫患者的联合用药仅在单药治疗不能控制癫痫发作时才考虑联合用药治疗，同时要合理选择联合使用的药物，避免不良反应的发生[29-31]。但本研究也有一定的不足，研究的样本量较少，且影响患者预后认知功能与生活质量的因素比较多，可能存在一定的研究偏倚性，还需要在下一步进行更加深入的量化分析。

总之，托吡酯联合拉莫三嗪用于治疗癫痫患者能显著改善认知功能，提高患者生活质量与治疗效果，且安全性较高。

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