Clinical study on anti-epileptic drug with B vitamins for the treatment of epilepsy after stroke

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Abstract. – OBJECTIVE: To study the clinical value of anti-epileptic drugs combined with B vitamins in the treatment of epilepsy after stroke.

PATIENTS AND METHODS: The study included 90 consecutive patients with epilepsy after stroke. Patients were randomly divided into groups of 30 each according to treatment: single-agent or combination anti-epileptic therapy with oxcarbazepine and sodium valproate (control group), anti-epileptic therapy with compound vitamin B tablets (observation group 1), and anti-epileptic therapy with vitamin B12 (mecobalamin) (observation group 2). After 12 months, treatment effects were assessed and compared among groups.

RESULTS: Compared with the control group, observation group 2 had better epilepsy control and observation group 1 had no difference in efficacy. New-onset stroke was seen in three cases (10%) of the control group and in two cases (6.7%) of observation group 1. This was not seen in observation group 2. In the control group and observation group 1, National Institutes of Health Stroke Scale (NIHSS) score significantly decreased after 6 months, but increased again at 12 months. Conversely, NIHSS score continuously decreased during follow-up in observation group 2. The plasma level of asymmetric dimethyl arginine (ADMA) gradually increased in the control group and observation group 1, but remained unchanged in observational group 2. The differences in NIHSS scores and plasma ADMA levels between the control and observation groups were statistically significant.

CONCLUSIONS: Anti-epilepsy drugs combined with B vitamins can improve epilepsy control after stroke and reduce new stroke occurrence. This effect may be associated with stability of plasma ADMA levels. Vitamin B12 may be better than vitamin B complex in the treatment of epilepsy after stroke.

Key Words: Anti-epileptic drugs, B vitamins, Epilepsy after stroke, Unsymmetrical dimethyl arginine.

Introduction

Epilepsy after stroke is a major form of senile epilepsy. Epileptic seizures and use of anti-epileptic drugs are independent risk factors for progression and recurrence of stroke1, and this poses additional difficulties in clinical treatment. In the viewpoint of many studies, reduction in B vitamins, especially vitamin B12, and folic acid levels2 may lead to metabolic disorders of homocysteine (Hcy), formation of high Hcy levels, and increased incidence of thrombosis3. B vitamins in the form of co-enzymes, which are involved in carbohydrate, lipid, protein, and nucleic acid metabolism, could affect the development and function of the nervous system4. B vitamin deficiency could decrease normal neurotransmission between synapses while increasing the excitability of neurons; this becomes the underlying cause of epilepsy5. At the same time, B vitamin deficiency has different degrees of effect on emotion, learning, memory, movement, balance, and cognitive function6. Exogenous B vitamin supplements could block excessive DNA methylation during aging degradation of the nervous system7. Studies on exogenous B12 vitamin supplements combined with anti-epileptic drugs in the treatment of different types of epilepsy have varying results8. At present, there is no concrete understanding of the benefits of prophylactic use of vitamin B12 in epilepsy treatment. Based on this fact, this randomized controlled trial aimed to compare the clinical effect of B vitamin supplementation in the treatment of epilepsy after stroke.

Patients and Methods

Patients

A total of 90 consecutive patients diagnosed with epilepsy after stroke in our hospital between
June 2012 and June 2015 were eligible for inclusion in this study. The diagnosis and treatment of epilepsy after stroke were in accordance with the National Institute for Health and Care Excellence (NICE) guidelines in 2012. Inclusion criteria were: age 18-75 years; primary occurrence of acute cerebral apoplexy without disturbance in consciousness and need for ventilatory support; no history of previous epilepsy; complete clinical data; good compliance with anti-epileptic and vitamin supplement therapies. Exclusion criteria were: history of brain tumor; brain trauma; surgery; radiation therapy; existing cognitive dysfunction; severe co-morbid diseases of the heart, liver, lungs, kidneys; other organ dysfunction; nutritional metabolic disease and blood disease; discontinuation of treatment due to adverse drug reaction; simultaneous participation in other studies. The study was approved by the Ethics Committee of our hospital. Informed consent was obtained from patients and their family members. According to the order of admission and using a random number method, patients were assigned to three groups, which were composed of 30 patients each: control group, observation group 1, and observation group 2.

Methods

The control group was given single-agent or combination anti-epileptic therapy with oxcarbazepine and sodium valproate. Oxcarbazepine (Trileptal; Novartis Pharmaceutical Co., Ltd., Origgio, VA, Italy; Approval No. H20130015; 0.15 g × 50 tablets) was given at a starting dose of 0.6 g per day divided into two doses; the dose was increased by 0.6 g weekly and daily maintenance dose ranged from 0.6 to 2.4 g. Sodium valproate (Hunan Xiangzhong Pharmaceutical Co. Ltd., Hunan Sheng, China; specification 0.2 g × 100 tablets, batch number 110514) was given at 0.2 g thrice daily. Observation group 1 were administered the above mentioned anti-epileptic drugs with additional compound vitamin B tablets (Lisheng; Tianjin Lisheng Pharmaceutical Co. Ltd., Tianjin, China; Approval No. H12020233; each tablet contained 3 mg vitamin B1, 1.5 mg vitamin B2, 0.2 mg vitamin B6, 10 mg nicotinamide, and 1 mg calcium pantothenate; 100 tablets per bottle) at 1-3 tablets single-dose once daily. Observation group 2 were administered the above mentioned anti-epileptic drugs with additional oral vitamin B12 or methylcobalamin (Methylcobalamin; China Weicai Pharmaceutical Co. Ltd., Zhengzhou, Henan, China; specification 0.5 × 20 mg tablets; batch number H20030812) at 0.5 mg once daily. Both anti-epileptic drugs and vitamin B12 were taken for 12 months. During epilepsy treatment with these agents, drug doses were reasonably adjusted according to characteristic of epilepsy onset. Routine blood tests, liver, and kidney function, electrolytes, etc. were tested periodically. Adverse reactions were monitored and drugs were withdrawn as necessary.

Study Variables

After a follow-up period of 12 months, the groups were compared in terms of level of epilepsy control, new occurrence of cerebral apoplexy, National Institutes of Health Stroke Scale (NIHSS) score, and plasma asymmetric dimethyl arginine (ADMA) levels. Epilepsy control was assessed according to the degree of decrease in frequency of epileptic seizure: ≥ 70% as effective, 50-69% as effective, and < 49% as ineffective. New occurrence of cerebral apoplexy was diagnosed by clinical symptoms and signs of stroke by computed tomography or magnetic resonance imaging. The NIHSS contained 15 items and was evaluated on results that were tabulated and recorded within 2 min; a higher score indicated a more severe symptom. Plasma ADMA levels were measured by high performance liquid chromatography (HPLC) kit (Jiangsu Biyuntian Technology Co., Ltd., Jiangsu, China), in strict compliance with the manufacturer’s instructions.

Statistical Analysis

The SPSS 20.0 software (SPSS Inc., Armonk, NY, USA) was used for statistical analyses. The collected data were presented as mean ± standard deviation (SD) and as number of cases or percentage. Comparison between groups was by single-factor analysis of variance. Pair-wise comparison was by LSD-t-test (Fisher’s least significant difference t-test). Comparison within groups for repeated measurement data was by analysis of variance, whereas comparison between groups was by X²-test or Fisher’s exact probability method, as appropriate. Sum of ranks test was used for ranked data. p < 0.05 was assigned as statistically significant.

Results

Epilepsy Control

The baseline characteristics of the three groups were comparable (Table I). Epilepsy control in observation group 2 was significant-
ly better than that in the control group (Z = 4.356, \(p = 0.037\)), but did not differ from that in observation group 1 (Z = 1.002, \(p = 0.317\)) (Table II).

**New Occurrence of Cerebral Apoplexy**

In the control group, new occurrence of cerebral apoplexy was seen in three cases (10.0\%) at 6, 8, and 12 months after treatment, respectively. In observational group 1, new cerebral apoplexy occurred in two cases (6.7\%) after 8 and 10.5 months of treatment, respectively. No new occurrence of cerebral apoplexy was seen in observational group 2.

**NIHSS Score and ADMA Level**

In the control group and observation group 1, NIHSS score significantly decreased after 6 months, but increased again at 12 months. In contrast, NIHSS score continuously decreased during follow-up in observation group 2; the difference was statistically significant (\(p < 0.05\)). The plasma level of ADMA increased gradually in the control group and observation group 1, but remained unchanged in observational group 2. Differences were statistically significant (\(p < 0.05\)) (Table III).

**Discussion**

Long-term anti-epileptic therapy after cerebral apoplexy is needed in patients with at least two early-onset epilepsy diseases, those with late-onset epilepsy and those with status epilepticus. The choice of anti-epileptic drugs in patients with epilepsy after stroke should be based on overall consideration of the complexity of the illness and other concurrent diseases. As pointed out by the Antiepileptic Drug Application Expert Consensus by the Electroencephalogram and Epileptology Group of the neurology branch of the Chinese Medical Association, lamotrigine or oxcarbazepine were the first treatment of choice in elderly patients with epilepsy without complications, whereas lamotrigine or levetiracetam could be chosen as therapy for those with other accompanying diseases. The mechanism of action of oxcarbazepine includes reduction of the activity of voltage-dependent sodium channels, inhibition of the release of excitatory neurotransmitters, mainly glutamate, increase of gamma-aminobutyric acid (GABA) levels, alleviation of cell edema, etc. Oxcarbazepine
is mainly used for intractable epilepsy, including partial and systemic seizures, and it does not affect the normal electrical activity of nerve cells. On the other hand, sodium valproate is the first line anti-epileptic drug for absence and systemic rigidity clonus seizures. It easily penetrates the blood-brain barrier and exerts its anti-epileptic effect by inhibiting aminobutyric acid invertase and butyl aldehyde acid dehydrogenase, by adjusting differentiation, survival and reshaping of neurons, and by affecting protein kinase signal transduction pathways activated by mitogen. The hypothesis of this research was that supplement of B vitamins was effective in anti-epilepsy and anti-apoplexy treatment. Vitamin B12 is involved in the synthesis and maintenance of the myelin sheath surrounding nerve cell, as well as in red blood cell synthesis. It plays a key role in cell division and growth and is closely correlated to folic acid. Some scholars suggested that compound vitamins and vitamin B12 were equally effective. This present work showed a similar result; also, supplementation with vitamin B12 resulted in better epilepsy control than anti-epileptic drugs alone. These data confirmed that supplementation of B vitamins has certain benefits in anti-epilepsy treatment. In addition, the varying occurrence of new-onset stroke among the groups indicated that vitamin B supplementation had certain beneficial effect on the prognosis of apoplexy. The results of NIHSS scores among groups during follow-up suggested that long-term anti-epileptic therapy may increase the risk of apoplexy and aggravate illness. The plasma ADMA levels in the control group and observation group 1 increased, whereas the level in observation group 2 remained unchanged. ADMA is an endogenous nitric oxide (NO) synthase inhibitor that causes endothelial dysfunction and participates in the pathogenesis and progression of atherosclerosis. The increase in plasma ADMA level and decrease in NO synthesis may be correlated with increase in Hcy levels, which have been confirmed by many researches to be closely related with the development of heart disease and cerebrovascular illnesses.

Conclusions

In patients with epilepsy after cerebral apoplexy, anti-epileptic drug therapy combined with B vitamin supplementation could improve epilepsy control and reduce new-onset stroke. Vitamin B12 may be better than vitamin B compound. These results may be correlated with stability in plasma ADMA levels.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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