doi.org/10.36721/PJPS.2023.36.1.SP.295-300.1

Analysis of the effect of sodium valproate combined with carbamazepine on improving cognitive function and self-care in patients with epilepsy

Dandan Wei and Sulian Gu*
Department of Neurology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

Abstract: To examine how sodium valproate and carbamazepine improve cognitive function and self-care in Epilepsy Patients (EP). Our facility collected 150 EP patients from September 2020 until June 2022. 70 patients received carbamazepine as the control group, and 80 received it with sodium valproate as the observation group. Both groups recorded EP attack frequency and duration following treatment to compare clinical efficacy. The Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF) were measured before and after treatment, adverse effects were counted, and the patient's ability to perform activities of daily living and activities was assessed by Montreal Cognitive Assessment (MOCA), Activities of Daily Life (ADL), and Barthel Index (BI). The observation group had fewer EP episodes and shorter EP episodes than the control group ($P<0.05$), and the total effective rate of treatment was greater. After treatment, Nerve Growth Factor and Brain Derived Neurotrophic Factor were higher in the observation group than in the control group ($P<0.05$). The observation group had fewer adverse effects than the control group ($P<0.05$). The observation group outperformed the control group in MOCA, ADL, and BI after treatment ($P<0.05$). Valproate with carbamazepine can reduce EP attacks and improve clinical efficacy and safety.

Keywords: Sodium valproate, carbamazepine, epilepsy, self-care ability, cognitive function.

INTRODUCTION

Epilepsy (EP), commonly known as “sheep horn wind” or “sheep epilepsy”, is a common clinical neurological disorder. As of 2017, the number of patients with EP in China alone has exceeded 10 million cases, with an average of more than 400,000 new cases per year (Falco-Walter, 2020). Studies have shown that abnormalities mainly cause EP in the brain due to various causes, such as abnormal excitation and hyper synchronization of brain nerve cells (Kanner and Bicchi, 2022). As a chronic lesion, EP is characterized by recurrent attacks, long disease duration, and a high disability rate, posing a severe threat to patients' physical and mental health (Perucca *et al*., 2020). Therefore, it is essential to have and understand the effective treatment options for EP as soon as possible to safeguard patients' health.

The ideal clinical treatment for EP is complete control of patients’ EP episodes, and pharmacotherapy is currently the preferred method of EP treatment (Loscher *et al*., 2020). However, due to the large number of drugs available for the clinical treatment of EP, there is still some controversy as to which drug is more effective (Thijs *et al*., 2019). Sodium valproate is a nitrogen-free, broad-spectrum anti-EP agent that is wholly and rapidly absorbed orally and has varying degrees of antagonistic effects against convulsions induced by various methods (Zhu *et al*., 2022). Carbamazepine is also a clinical treatment for EP disease and neuropathic pain and is particularly more effective than other anti-EP drugs for complex partial seizures (Beydoun *et al*., 2020). A review of previous data showed that the combination of sodium valproate with carbamazepine had significant efficacy in the treatment of EP (Knights and Finlay, 2014, Gierbolini *et al*., 2016), but there are few studies on the improvement of patients’ self-care ability and other indicators, and the research data are not yet complete. Therefore, this study was conducted to analyze the effect of sodium valproate combined with carbamazepine on the improvement of cognitive function and self-care ability of EP patients, to provide more comprehensive reference and guidance for future clinical treatment.

MATERIALS AND METHODS

Ethical approval

Ethical approval was taken from the institute of bioethical safety committee and written consent from patients was also taken.

Clinical data

One hundred fifty patients with EP treated in our hospital from September 2020 to June 2022 were collected. Among them, 70 patients received carbamazepine treatment and were regarded as the control group, and 80 received carbamazepine combined with sodium valproate treatment and were regarded as the observation group.

*Corresponding author: e-mail: gusulian1985@163.com

Inclusion and exclusion criteria

Inclusion criteria

Patients all met the diagnostic criteria for EP (Pack, 2019), and all had episodes of EP; case data were well documented, and there were no allergies to study drugs. Exclusion criteria: those with a history of brain-cranial injury disease, cerebrovascular disease, abnormal liver and kidney function; patients during pregnancy or lactation; those with other combined severe diseases; those with difficulty in communication with impaired consciousness.

Treating methods

Control group

treatment with carbamazepine (Guangdong Luofuoshan National Pharmaceutical Co., Ltd., H44022411) starts at a dose of 0.1g/d, 2-3 times/d, and increases by 0.1g daily from the 2nd d until efficacy occurs, with the highest dose not exceeding 1.2g/d. Observation group: sodium valproate (Taiwan Biotech Co., Ltd., HC20120017) was added to the control group at an initial dose of 5-10 mg/kg, which was increased in increments after one week until the seizures could be controlled. When the daily dosage exceeds 2500 mg, it should be divided into smaller doses, with the maximum daily amount not exceeding 30 mg/kg. Both groups were treated continuously for 3 months.

Nursing methods

Psychological nursing

Explain disease knowledge to patients, comfort patients, and eliminate their negative psychology to the maximum extent. (2) Blood pressure monitoring: after using the drug, patients' blood pressure should be monitored at any time to observe whether there are any adverse reactions. If there is any abnormality, report to the doctor in time and adjust the drug dosage. (3) Dietary care: maintain a light, easily requirements: treat patients with patience and care, walk lightly, operate lightly, communicate lightly, close the door with your hand, pay attention to patients' emotional changes at any time, try to meet their reasonable requirements, and actively dispel their negative emotions, to improve treatment compliance and establish a harmonious doctor-patient relationship. (6) Health lectures are held to promote health knowledge: patients are given easy-to-understand explanations about their illnesses and are informed of what they need to pay attention to in their daily diet, work, and rest. Through typical successful cases, patients are motivated to actively cooperate with the medical staff and build confidence in their treatment, digestible, high-calorie, high-protein, low-salt, low-fat diet, and increase fibre intake appropriately to avoid constipation and forceful defecation in constipated individuals to prevent accidents. (4) Improving the ward environment: Create a neat, quiet, comfortable and harmonious inpatient environment for patients. (5) Smile service can meet patients' reasonable thereby shortening the treatment time and improving the efficiency and quality of treatment.

Outcome measures

Clinical efficacy

Markedly effective: clinical symptoms and disease episodes were effectively controlled, seizure frequency decreased by greater than 70% compared to the pre-treatment period, and EEG showed good improvement. Effective: Clinical symptoms improved significantly after treatment, with a greater than 40%-70% decrease in seizure frequency and a corresponding improvement in EEG. Ineffective: There was no noticeable change and no significant improvement in seizure frequency after treatment. Total effective rate = (effective + effective) cases/total × 100%. (2) The frequency and duration of disease attacks after treatment were recorded for both groups. (3) Before and after treatment, 5 mL of fasting anterior venous blood was drawn from patients' elbows, and nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) were measured by enzyme-linked immunosorbent assay (ELISA). (4) The adverse reactions in treatment were counted, such as liver function impairment, rash, gastrointestinal discomfort, etc. (5) The Montreal Cognitive Assessment (MoCA) (Kang *et al*., 2018) was used before and after treatment to assess cognitive function in both groups, containing attention and concentration, executive ability, memory, language, visuospatial skills, abstract thinking, computation, and orientation, with higher scores indicating better cognitive function. Activities of Daily Living (ADL) (Pedulla *et al*., 2020) was used to assess patients' viability, and ADL contains 10 items of eating, bathing, grooming, dressing, bowel control, toileting, table and chair turning, walking on level ground, and walking up and down stairs, with a total score of 100, with higher scores indicating better self-care ability. The Barthel index evaluated patients' activity (Shah *et al*., 1989), including 10 examination items, with a total score of 100: the higher the score, the better the activity.

STATISTICAL ANALYSIS

The data results were assessed statistically by SPSS 23.0 statistical software. The counting data were expressed as (rate) and compared by the chi-square test, while the measurement data were expressed as (mean ± standard deviation) and compared by the t-test. $P<0.05$ was considered a statistically significant difference.

RESULTS

General datasheet

General data such as gender, age, duration of EP, history of smoking and history of alcohol consumption were collected and statistically calculated for both groups, and the results showed no statistically apparent differences

between groups (P>0.05), suggesting that the two groups were comparable table 1.

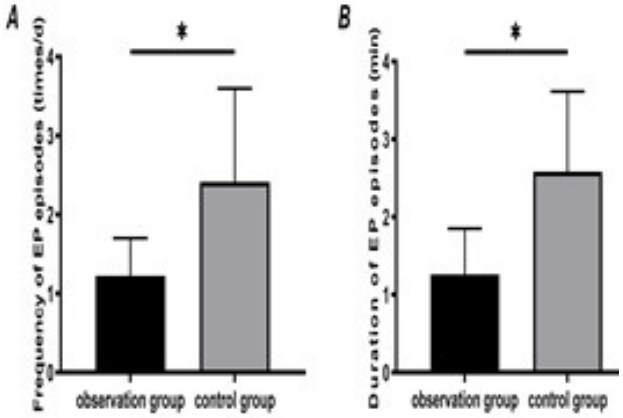

Fig. 1: EP seizure (A) Frequency of EP episodes. (B) Duration of EP episodes. *P<0.05.

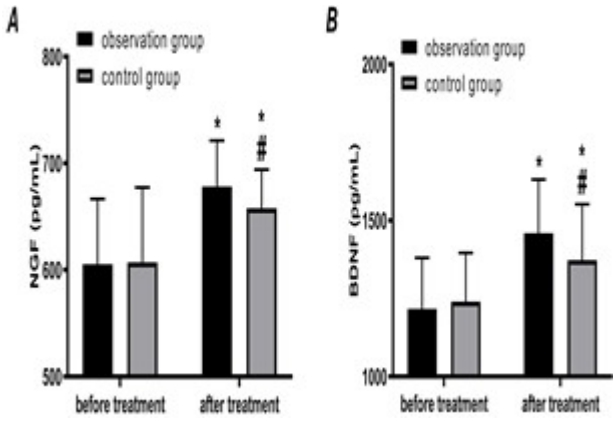

Fig. 2: Nerve injury conditions. (A) Comparison of NGF. (B) Comparison of BDNF. *: *vs.* before treatment, P<0.05; #: *vs.* observation group, P<0.05.

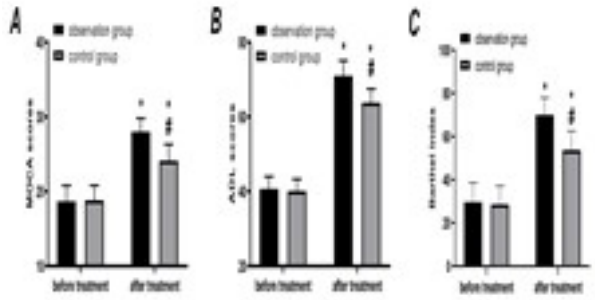

Fig. 3. Objective scoring results. (A) Comparison of MOCA scores. (B) Comparison of ADL scores. (C) Comparison of BI. *: *vs.* before treatment, P<0.05; #: *vs.* observation group, P<0.05.

Clinical efficacy

The clinical efficacy of the two groups was assessed. The percentage of patients whose clinical symptoms were effectively controlled was higher in the observation group than in the control group, with an inefficiency rate of 3.75% and an inefficiency rate of 12.86% in the control group. The results of statistical analysis manifested that the total effective rate of treatment in the observation group was higher than that in the control group (P<0.05), table 2.

EP seizure

It was seen that the number of EP episodes and the duration of EP episodes in the observation group were lower than those in the control group and the difference was statistically remarkable (P<0.05) (fig. 1).

Nerve injury conditions

Before treatment, the results of NGF and BDNF assays were relatively similar between the two groups and the differences were not remarkable (P>0.05). After treatment, the levels of NGF and BDNF were higher in the observation group compared with the control group, and the difference was remarkable (P<0.05). The results of NGF and BDNF assays were higher in both groups after treatment compared with those before treatment (P<0.05) (fig. 2).

Adverse reactions

The incidence of total adverse reactions was 7.50% in the observation group and 18.57% in the control group, which denoted that the incidence of adverse reactions was lower in the observation group than in the control group (P<0.05) (table 3).

Objective scoring results

Before treatment, there was no statistically remarkable difference in MOCA and ADL scores compared with BI in both groups (P>0.05). While after treatment, MOCA and ADL scores and BI increased in both groups. The results of all the scores in the observation group were higher than those in the control group (P<0.05) (fig. 3).

DISCUSSION

This study used valproate sodium and carbamazepine to treat patients with EP. We found that the clinical efficacy of patients was improved. The number and duration of EP attacks were effectively suppressed, suggesting that valproate sodium in combination with carbamazepine significantly affects treating EP. Similarly, this is consistent with the results of previous studies (Nevitt *et al*., 2018a, Pino *et al*., 2021), which can corroborate the results of the current experiment. It is well known that sodium valproate is a nitrogen-free broad-spectrum antiepileptic drug and one of the common drugs used in clinical practice for the treatment of EP and that the drug is mainly distributed in the extracellular fluid and mostly bound to plasma proteins in the blood (Li *et al*., 2019). Carbamazepine is a common psychotropic drug that has the effect of stabilizing overexcited nerve cell membranes and inhibiting recurrent nerve firing (Nevitt *et al*., 2018b).

Table 1: General datasheet

	N	Male / Female	Age	Duration of disease (years)	Smoking Yes / No	Drinking alcohol Yes / No
Observation group	80	48(60.00)/32(40.00)	47.7±4.0	4.5±1.4	39(48.75)/41(51.25)	53(66.25)/27(33.75)
Control group	70	43(61.43)/27(38.57)	47.5±4.2	4.4±1.7	32(45.71)/38(54.29)	47(67.14)/23(32.86)
χ^2/t		0.032	0.298	0.395	0.138	0.013
P		0.858	0.766	0.694	0.710	0.908

Table 2: Clinical efficacy

	N	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	80	45(56.25)	32(40.00)	3(3.75)	96.25
Control group	70	26(37.14)	35(50.00)	9(12.86)	87.14
χ^2					4.207
P					0.040

Table 3: Adverse reactions

	Rash	Gastrointestinal discomfort	Diarrhea	Impaired liver function	Hair loss	Incidence of adverse reactions
Observation group	2(2.50)	1(1.25)	1(1.25)	1(1.25)	1(1.25)	7.50
Control group	3(4.29)	2(2.86)	4(5.71)	2(2.86)	2(2.86)	18.57
χ^2						4.137
P						0.042

Meanwhile, carbamazepine inhibits electrical activity in the anterior ventral nucleus of the thalamus of patients, limits the spread of abnormal discharges in EP-causing lesions, reduces the transmission of excitatory impulses by synapses in the central nervous system, and closes voltage-dependent sodium channels (Nolan *et al*., 2016). In patients with EP, antiepileptic drugs can reduce sodium channel sensitivity in the body and affect the transmission of electrical signals in brain tissue, thus exerting control of EP (Santalucia *et al*., 2022). We believe that the reasons for the superior clinical outcome of patients in the observation group are: Sodium valproate mainly acts on the enzymatic reaction process of abnormal primary neuronal cells to curb neuronal cell firing, while carbamazepine directly intervenes to stabilize cell membranes and simultaneously curb the spread of abnormal firing to surrounding areas, and the two drugs can play a synergistic role, thus more effectively promoting the improvement of various clinical symptoms and alleviating the condition of patients with EP (Milligan, 2021).

Besides, the role of NGF and BDNF as essential indicators for observing the degree of nerve damage during EP pathology has been demonstrated in several studies (Ferraguti *et al*., 2022). Thus, we also further observed the difference in the levels of NGF and BDNF between both groups of patients, and the results then showed higher levels in the observation group after treatment, which further illustrated the improvement of EP symptoms in the observation group and verified the accuracy of the above experimental results. Finally, the research group had fewer adverse reactions, which suggests that we have a higher safety profile for valproate combined with carbamazepine.

In previous studies, valproate and carbamazepine have been shown to cause more pronounced hepatic and renal reactions under long-term use, increasing drug toxicity in patients and affecting the effectiveness of treatment (Kaplan and Demir, 2021). And when the two are used in combination, the dosage of each drug is reduced, which can reduce the damage of drug toxicity to patients. It also reduces drug resistance development, making the treatment more effective (Nevitt *et al*., 2022).

On the other hand, we also found more significant improvements in objective functional scores after treatment in both groups in the current study, and there were more significant hints of MOCA, ADL scores and BI in the control group compared to previous studies (Novak *et al*., 2022), which we believe is related to more targeted care services. During the long treatment cycle of EP, patients commonly exhibit agitation, anxiety and depression, and factors such as mental stress, emotional excitement, and adverse stimuli can trigger the onset of the disease (Montano-Lozada *et al*., 2021).

Therefore, psychological counselling of patients is of great importance. In addition, blood pressure fluctuations can affect drug therapy's effectiveness (Shawahna, 2021). Nursing also needs to be taken to make patients aware of

the importance of blood pressure control and to help them train in self-control and participate in developing and implementing their own treatment and care plans. In the end, a proper diet and nutritional intake also helped EP patients to be in a better and ideal state of recovery, which was not only more conducive to the treatment effect but also might inhibit the adverse effects, which was presumably one of the reasons for the lower adverse effects in both groups in this study.

Nevertheless, there may be some result bias due to the small number of cases included in this study and the short follow-up period. We need to conduct a randomized controlled trial for confirmation as soon as possible in the follow-up. Moreover, we also need to analyze the optimal dose of valproate combined with carbamazepine to provide more reliable clinical advice.

CONCLUSION

Valproate combined with carbamazepine for the treatment of EP can effectively enhance the clinical efficacy and suppress the attacks of EP while having a high safety profile and a high clinical application value. In the future, sodium valproate combined with carbamazepine is recommended as the preferred treatment for EP in clinical practice, thus providing a more reliable guarantee for patients' health.

REFERENCES

Beydoun A, Dupont S, Zhou D, Matta M, Nagire V and Lagae L (2020). Current role of carbamazepine and oxcarbazepine in the management of epilepsy. *Seizure,* **83**: 251-263.

Falco-Walter J (2020). Epilepsy-definition, classification, pathophysiology and epidemiology. *Semin. Neurol.,* **40**(6): 617-623.

Ferraguti G, Terracina S, Micangeli G, Lucarelli M, Tarani L, Ceccanti M, Spaziani M, Dorazi V, Petrella C and Fiore M (2022). NGF and BDNF in pediatrics syndromes. *Neurosci. Biobehav. Rev.,* **145**: 105015.

Gierbolini J, Giarratano M and Benbadis SR (2016). Carbamazepine-related antiepileptic drugs for the treatment of epilepsy - a comparative review. *Expert Opin Pharmacother.,* **17**(7): 885-888.

Kang JM, Cho YS, Park S, Lee BH, Sohn BK, Choi CH, Choi JS, Jeong HY, Cho SJ, Lee JH and Lee JY (2018). Montreal cognitive assessment reflects cognitive reserve. *BMC Geriatr.,* **18**(1): 261.

Kanner AM and Bicchi MM (2022). Antiseizure medications for adults with epilepsy: A review. *JAMA,* **327**(13): 1269-1281.

Kaplan YC and Demir O (2021). Use of phenytoin, phenobarbital carbamazepine, levetiracetam lamotrigine and valproate in pregnancy and breastfeeding: Risk of major malformations, dose-dependency, monotherapy vs polytherapy, pharmacokinetics and clinical implications. *Curr Neuropharmacol.,* **19**(11): 1805-1824.

Knights MJ and Finlay E (2014). The effects of sodium valproate on the renal function of children with epilepsy. *Pediatr. Nephrol.,* **29**(7): 1131-1138.

Li J, Yang D, Zhao D, Li N and Lin W (2019). Efficacy of phenobarbital and sodium valproate in treating convulsive epilepsy in rural northeast China. *Seizure,* **71**: 207-213.

Loscher W, Potschka H, Sisodiya SM and Vezzani A (2020). Drug resistance in epilepsy: Clinical impact, potential mechanisms and new innovative treatment options. *Pharmacol. Rev.,* **72**(3): 606-638.

Milligan TA (2021). Epilepsy: A clinical overview. *Am. J. Med.,* **134**(7): 840-847.

Montano-Lozada JM, Lopez N, Espejo-Zapata LM, Soto-Anari M, Ramos-Henderson, M, Caldichoury-Obando N and Camargo L (2021). Cognitive changes in patients with epilepsy identified through the MoCA test during neurology outpatient consultation. *Epilepsy Behav.,* **122**: 108158.

Nevitt SJ, Marson AG, Weston J and Tudur Smith C (2018a). Sodium valproate versus phenytoin monotherapy for epilepsy: An individual participant data review. *Cochrane Database Syst. Rev.,* **8**(8): CD001769.

Nevitt SJ, Sudell M, Cividini S, Marson AG Tudur Smith C (2022). Antiepileptic drug monotherapy for epilepsy: A network meta-analysis of individual participant data. *Cochrane Database Syst. Rev.,* **4**(4): CD011412.

Nevitt SJ, Tudur Smith C, Weston J and Marson AG (2018b). Lamotrigine versus carbamazepine monotherapy for epilepsy: An individual participant data review. *Cochrane Database Syst. Rev.,* **6**(6): CD001031.

Nolan SJ, Tudur Smith C, Weston J and Marson AG (2016). Lamotrigine versus carbamazepine monotherapy for epilepsy: An individual participant data review. *Cochrane Database Syst Rev.,* **11**(11): CD001031.

Novak A, Vizjak K, Gacnik A, Rakusa M (2022). Cognitive impairment in people with epilepsy: Montreal cognitive assessment (MoCA) as a screening tool. *Acta Neurol Belg*., pp.s13760-022.

Pack AM (2019). Epilepsy Overview and Revised Classification of Seizures and Epilepsies. *Continuum (Minneap Minn),* **25**(2): 306-321.

Pedulla L, Tacchino A, Podda J, Bragadin NMM, Bonzano L, Battaglia MA, Bove M, Brichetto G, Ponzio M (2020). The patients' perspective on the perceived difficulties of dual-tasking: Development and validation of the Dual-task Impact on Daily-living Activities Questionnaire (DIDA-Q). *Mult. Scler. Relat. Disord.,* **46**: 102601.

Perucca P, Bahlo M and Berkovic SF (2020). The genetics of epilepsy. *Annu Rev Genomics Hum Genet.,* **21**: 205-

230.

Pino EJ, Pucheu F, Alvarado F, Gomez B, De Diego M, Mennickent S, Aguayo C, Pena C and Rodriguez A (2021). Carbamazepine biosensor development for epilepsy patient screening. *Annu Int Conf IEEE Eng Med. Biol. Soc.,* pp.1531-1534.

Santalucia R, Vilain C, Soblet J, De Laet C, Vuckovic A, Konic J and Aeby A (2022). Carbamazepine efficacy in a severe electro-clinical presentation of SLC13A5-epilepsy. *Ann. Clin. Transl. Neurol.,* **9**(7): 1095-1099.

Shah S, Vanclay F, Cooper B (1989). Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J. Clin. Epidemiol.,* **42**(8): 703-9.

Shawhna R (2021). Using a mixed method to develop consensus-based aims, contents, intended learning outcomes, teaching and evaluation methods for a course on epilepsy for postgraduate or continuing education in community health nursing programs. *BMC Med. Educ.,* **21**(1): 572.

Thijs RD, Surges R, Obrien TJ, Sander JW (2019). Epilepsy in adults. *Lancet.,* **393**(10172): 689-701.

Zhu Y, Yang J and Zhu X (2022). Combined effects of levetiracetam and sodium valproate on paediatric patients with epilepsy: A systematic review and meta-analysis. *Seizure,* **95**: 17-25.