ORIGINAL ARTICLE

Effects of sodium valproate combined with levetiracetam in treatment of children epilepsy and its influences on serum S-100β and high mobility group box-1

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Received: June 12, 2020 **Accepted:** August 10, 2020 **Online Published:** August 25, 2020
DOI: 10.5430/dcc.v7n1p12 **URL:** https://doi.org/10.5430/dcc.v7n1p12

ABSTRACT

Objective: To explore the effects of sodium valproate combined with levetiracetam in the treatment of children epilepsy, and its influences on serum S-100β and high mobility group box-1 (HMGB-1) in children with epilepsy.

Methods: A total of 160 children who were diagnosed as epilepsy in Baogang Hospital of Inner Mongolia from July 2016 to October 2018 were selected as research objects. They were randomly divided into the study group (n = 80) and the control group (n = 80) by the random number table method, i.e., they were treated with sodium valproate combined with levetiracetam and sodium valproate alone, respectively. After 16 weeks of treatment, the effective rates of epileptic seizure treatment and the improvement of epileptiform discharge were evaluated, and chi-square test was used for statistical comparison. The related indicators, including serum tumor necrosis factor-α (TNF-α), hypersensitive C-reactive protein (hs-CRP), homocysteine (Hcy), haematocrit (HCT), erythrocyte sedimentation rate (ESR), serum S-100β and HMGB-1, were measured before and after treatment. Paired t-test was used for the comparison in the above indicators within a group before and after treatment; group t-test was used for the comparison between two groups. Chi-square test was used for the comparison in the rate of adverse reactions during treatment between two groups. The study was approved by Ethics Committee of Baogang Hospital (Approval No.: BG201606073), and all children's guardians were required to sign informed consent forms for clinical study. There were no statistically significant differences between two groups in general clinical data ($p > .05$), such as sex constituent ratio, age, the course of disease, the frequency of epileptic seizure per year before treatment, the incidence of epileptiform discharge before treatment and the constituent ratio of types of epileptic seizure, etc.

Results: 1) After treatment, the effective rates of epileptic seizure treatment and the improvement of epileptiform discharge in the study group were 92.5% (74/80) and 85.0% (68/80) respectively, which were both significantly higher than those in the control group [68.8% (55/80) and 58.8% (47/80)], and the differences were statistically significant (χ^2 = 14.444, 13.635; $p < .001$). 2) In the study group, the levels of serum TNF-α, hs-CRP and Hcy, as well as HCT and ESR after treatment were (53.1 $\pm$ 14.0) pg/ml, (5.0 $\pm$ 2.5) mg/L, (12.5 $\pm$ 3.1) μmol/L, (38.1 $\pm$ 5.1)% and (3.0 $\pm$ 0.5) mm/h respectively, which were all significantly lower than those [(107.9 $\pm$ 17.8) pg/ml, (10.1 $\pm$ 2.5) mg/L, (42.2 $\pm$ 5.8) μmol/L, (45.3 $\pm$ 4.5)% and (5.2 $\pm$ 0.6) mm/h] before treatment, and all the differences were statistically significant (t = 21.644, 12.902, 40.393, 9.468, 25.194; $p < .001$). In the control group, the levels of serum TNF-α, hs-CRP and Hcy, as well as HCT and ESR after treatment were (60.6 $\pm$ 17.8) pg/ml, (8.2 $\pm$ 2.2) mg/L, (15.2 $\pm$ 3.1) μmol/L, (40.2 $\pm$ 3.4)% and (4.5 $\pm$ 0.6) mm/h respectively, which were all significantly lower than those [(112.4

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± 14.3) pg/ml, (9.3 ± 3.8) mg/L, (41.1 ± 2.8) μmol/L, (44.6 ± 5.5)% and (5.4 ± 0.8) mm/h] before treatment, and all the differences were statistically significant (t = 20.292, 2.241, 55.456, 3.320, 8.050; p < .05). After treatment, the above indicators in the study group were all significantly lower than those in the control group, and all the differences were statistically significant (t = 2.962, 8.595, 5.508, 3.064, 17.178; p < .05). 3) In the study group, the levels of serum S-100β and HMGB-1 after treatment were (0.65 ± 0.38) μg/L and (5.3 ± 2.4) μg/L respectively, which were significantly lower than those [(0.91 ± 0.32) μg/L and (8.1 ± 2.0) μg/L] before treatment, and the differences were statistically significant (t = 4.681, 8.020; p < .001). In the control group, the levels of serum S-100β and HMGB-1 after treatment were (0.78 ± 0.27) μg/L and (6.4 ± 2.2) μg/L respectively, which were significantly lower than those [(0.88 ± 0.25) μg/L and (7.9 ± 1.7) μg/L] before treatment, and the differences were statistically significant (t = 2.431, p = .016; t = 4.826, p < .001). After treatment, the levels of serum S-100β and HMGB-1 in the study group were significantly lower than those in the control group, and the differences were statistically significant (t = 2.495, p = .014; t = 2.840, p = .005). 4) There was no significant difference between two groups in the rate of adverse reactions, such as nausea, vomiting, poor appetite, dizziness, drowsiness, hepatic and renal injury during treatment (p > .05).

Conclusions: The efficacy of sodium valproate combined with levetiracetam is obviously better than that of sodium valproate alone in the treatment of children epilepsy. The children patients' serum S-100β and HMGB-1 are more significantly reduced, resulting in a lower rate of adverse reactions, which has a certain clinical value.

Key Words: Epilepsy, Sodium valproate, Levetiracetam, S-100β, HMGB-1 protein, Tumor necrosis factor-α, Haematocrit, Children

1. INTRODUCTION

Children epilepsy, a type of neurological syndrome which is commonly seen in individuals with the age ranging from 0 to 18, is caused by complicated etiological factors, recurrent seizures and clonic or temporary cerebral dysfunction. The pathogenesis of children epilepsy is complicated, and the main symptoms are sudden loss of consciousness, spasm and gatism. This disease can result in severe complications such as behavior disorder and abnormal development.[1] At present, the drug therapy (e.g., sodium valproate, carbamazepine etc.) is conventionally used in the clinical treatment of children epilepsy, but the curative effect and children compliance are so unsatisfactory that it is urgent to find a more effective treatment option for children epilepsy.[2] Levetiracetam is a novel anti-epileptic drug which has been used in the clinical treatment of children epilepsy in recent years, with a characteristic of obvious curative effects and less adverse reactions.[3] S-100β and HMGB-1 protein are serum markers of cerebral injury which have been studied the most recently, and they have an important predictive value of the curative effect and prognosis for children epilepsy.[4,5] This research is intended to explore the efficacy of sodium valproate combined with levetiracetam in the treatment of children epilepsy and the influences on S-100β and HMGB-1, in order to provide a reference for the clinical treatment of children epilepsy. The research results are reported as follows.

2. DATA AND METHODS

2.1 Research objects and grouping

A total of 160 children who were diagnosed as epilepsy in Baogang Hospital of Inner Mongolia from July 2016 to October 2018 were selected as research objects. They were randomly divided into the study group (n = 80) and the control group (n = 80) by the random number table method. The study was approved by Ethics Committee of Baogang Hospital (Approval No.: BG201606073), and all children's guardians were required to sign informed consent forms for clinical study.

2.2 Methods

2.2.1 *The diagnostic standards for children epilepsy*

The diagnosis of children epilepsy was performed according to "Expert consensus on the initial single drug therapy for the new diagnosis of epilepsy in children" established by Neurology Group of Pediatric Branch of Chinese Medical Association.[6]

2.2.2 *Inclusion and exclusion criteria*

Inclusion criteria of the research: children who were diagnosed as epilepsy according to the diagnostic standards of children epilepsy,[6] aged 3 to 14, receiving the epilepsy treatment for the first time. Exclusion criteria: children with cognitive and mental anomalies etc., who cannot cooperate with doctors during treatment and follow-up visits; with allergic reactions to sodium valproate and/or levetiracetam; with cardiac, hepatic, renal and other systemic diseases; whose parents refused to sign informed consent forms for the clinical study.

2.2.3 *Treatment methods of children epilepsy*

The children in the control group were given sodium valproate alone for treatment [Batch No.: 86904502000356, SANOFI (Hangzhou)]. The initial dose was 10 mg/ (kg·d), once daily, orally taken before bedtime. The dose was in-

creased by 5 mg/ (kg·d) weekly. The maintenance dose was 20-30 mg/ (kg·d), and the plasma concentration of sodium valproate with the maintenance dose was about 50-100 μg/ml. The course of treatment was 16 weeks in total, and the plasma concentration was monitored every two weeks. In combination with the plasma concentration and the frequency of epileptic seizure, it was acceptable to adjust the dosage of sodium valproate as follows: 1) If the plasma concentration of sodium valproate was close to the plasma concentration of sodium valproate with the maintenance dose and the epilepsy symptoms were relieved, it was acceptable to keep the current dose; if the symptoms were not relieved, it was needed to increase the dose by 5 mg/(kg·d) weekly and then measure the plasma concentration in 2 weeks. 2) If the plasma concentration of sodium valproate exceeded the plasma concentration of sodium valproate with the maintenance dose, it was necessary to decrease the dose by 5 mg/(kg·d) weekly to reach up to the plasma concentration of the maintenance dose; after the decrease, if the frequency of epileptic seizure was increased, it was needed to return to the original dose while monitoring hepatic and renal function simultaneously. The plasma concentration would be measured in two weeks. 3) If the plasma concentration of sodium valproate was lower than the plasma concentration of sodium valproate with the maintenance dose and the epilepsy symptoms were relieved, it was acceptable to keep the current dose; if the symptoms were not relieved, it was needed to increase the dose by 5 mg/(kg·d) weekly to reach up to the plasma concentration of sodium valproate with the maintenance dose and then measure the plasma concentration in 2 weeks. On the basis of the treatment given to the control group, the children in the study group were given levetiracetam in combination (Batch No.: YBH02302014, Zhenjiang Jingxin Pharmaceutical LLC.). The initial dose was 20 mg/(kg·d), two times a day, orally taken in the morning and at night. The dose was increased by 5 mg/(kg·d) every two weeks to reach up to the maintenance dose of 30-40 mg/(kg·d). The course of treatment was also 16 weeks. The adjustment principle of levetiracetam was identical to that of sodium valproate. Some experienced physicians of the same team would participate in the evaluation of the epilepsy symptoms in two groups of children in this research to provide a reference for dosage adjustment.

2.2.4 *The evaluation indexes of clinical efficacy*

1) The improvement rate of epileptic seizure treatment (%) = (1 - the average frequency of epileptic seizure after 16-week treatment/the average frequency of epileptic seizure before 16-week treatment) $\times$ 100%. Improved, effectual, going-better and ineffective treatment effects referred to the improvement rates after these children received 16-week treatment, i.e., 100%, $\geq$ 75%-100%, $\geq$ 50%-75% and < 50%, respectively.[7] The effective rate of epileptic seizure treatment (%) = (the number of children with improved, effectual, going-better treatment effects/the total number of children in this research) $\times$ 100%. 2) After 16-week treatment, improved, effectual and ineffective treatment effects of epileptiform discharge referred to the fact that the frequencies of epileptiform discharge were reduced by 100%, $\geq$ 50%-100% and < 50% in comparison to those before 16-week treatment.[7] The effective rate of the improvement of epileptiform discharge (%) = (the number of children with improved and effectual treatment effects of epileptiform discharge/the total number of children in this research) $\times$ 100%.

2.2.5 *The measurement of inflammation-related indicators as well as serum S-100β and HMGB-1*

Before and after treatment, 3 ml of elbow venous blood (fasting blood) was taken from each child in two groups, and EDTA was used for anti-coagulation. Each blood sample was centrifuged at the rotate speed of 3,000 r/min (Centrifugal radius: 10 cm) for 10 min by a Thermo Fisher centrifuge (Thermo Fisher, USA). The upper layer of serum was isolated, placed and frozen at -20 °C, for the measurement of inflammation-related indicators as well as serum S-100β and HMGB-1. 1) The measurement of inflammation-related indicators: ELISA kits for TNF-α, hs-CRP and Hcy (Batch No.: 1604018, 1606021, 1605014; Shanghai Renjie Biotechnology Co., Ltd.) were applied to the measurement. It was required to strictly follow the kit instructions to implement the operational procedures for the measurement of TNF-α, hs-CRP and Hcy. Wintrobe method was used to measure HCT and ESR of the whole blood sample from each subject in two groups. 2) The measurement of S-100β and HMGB-1: ELISA kits for S-100β and HMGB-1 (Batch No.: 1605023, 1601012; Shanghai Jianglai Biotechnology Co., Ltd.) were applied to the measurement. It was required to strictly follow the kit instructions to implement the operational procedures for the measurement of S-100β and HMGB-1.

2.2.6 *Adverse reactions*

The adverse reactions, such as nausea, vomiting, poor appetite, dizziness, drowsiness, hepatic and renal injury, were observed and recorded during the treatment in two groups of subjects.

2.3 Statistical analysis methods

SPSS 17.0 statistical software was applied to the statistical analysis of the data in this research. Ssize software was used to calculate the minimum sample size which met the statistical tests of the research. The measurement data, such as age, the course of disease, the frequency of epileptic seizure per year before treatment, serum TNF-α, hs-CRP, Hcy, HCT,

ESR, serum S-100β and HMGB-1, were represented by $\bar{X}\pm$ s. Group t-test was used for the comparison between two groups; paired t-test was used for the comparison within a group before and after treatment. The categorical data, such as sex constituent ratio, the incidence of epileptiform discharge before treatment, the constituent ratio of types of epileptic seizure, the effective rate of epileptic seizure treatment, the effective rate of the improvement of epileptiform discharge and the rate of adverse reactions, were represented by percentage (%). Chi-square test was used for the comparison between two groups. The two-sided test was adopted in all statistical tests, and the difference $p < .05$ was of statistical significance.

3. RESULTS

3.1 The comparison of clinical data between two groups of children

There were no statistically significant differences between two groups in general clinical data, such as sex constituent ratio, age, the course of disease, the frequency of epileptic seizure per year before treatment, the incidence of epileptiform discharge before treatment and the constituent ratio of types of epileptic seizure, etc. ($p > .05$). See Table 1 for the comparison of clinical data between two groups of children.

3.2 The comparison of the curative effect between two groups of children

After treatment, the effective rates of epileptic seizure treatment and the improvement of epileptiform discharge in the study group were both superior to those in the control group, and the differences were statistically significant ($p < .001$). See Table 2 for the comparison in the frequency of epileptic seizure and the improvement of epileptiform discharge after treatment between two groups of children.

3.3 The comparison of inflammation-related indicators between two groups of children

Before treatment, TNF-α, hs-CRP, Hcy, HCT and ESR were compared between two groups of children, and the differences were of no statistical significance ($p > .05$). In the comparison within each group, the above indicators after treatment were obviously lower than those before treatment, and the differences were statistically significant ($p < .05$); after treatment, in the comparison between two groups, the above indicators in the study group were obviously lower than those in the control group, and the differences were statistically significant ($p < .05$). See Table 3 for the comparison in serum TNF-α, hs-CRP, Hcy, HCT and ESR between two groups of children.

Table 1. The comparison of clinical data between two groups of children

Group	n	Gender [n (%)]		Age	The course of disease	The frequency of epileptic seizure per year before treatment	The incidence of epileptiform discharge before treatment	Types of epileptic seizure [n (%)]				
		Male	Female	(year-old, $\bar{x}\pm s$)	(year (s), $\bar{x}\pm s$)	(Time (s)/year, $\bar{x}\pm s$)	[n (%)]	Simple partial seizure	Complex partial seizure	Tonic-clonic seizure	Tonic seizure	Others
Study Group	80	47 (58.8)	33 (41.2)	7.0±1.5	1.9±0.7	2.7±1.3	50 (62.5)	38 (47.5)	20 (25.0)	11 (13.8)	7 (8.7)	4 (5.0)
Control Group	80	52 (65.0)	28 (35.0)	6.8±1.3	1.7±0.7	2.6±1.5	48 (60.0)	35 (43.8)	18 (22.5)	12 (15.0)	10 (12.5)	5 (6.2)
Test value		$\chi^2 = 0.662$		$t = 0.901$	$t = 1.807$	$t = 0.583$	$\chi^2 = 0.105$	$\chi^2 = 0.790$				
p value		.416		.368	.073	.561	.746	.851				

Note. The study group was made up of the children who received the treatment of sodium valproate combined with levetiracetam, and the control group consisted of the children who received the treatment of sodium valproate alone.

Table 2. The comparison in the frequency of epileptic seizure and the improvement of epileptiform discharge after treatment between two groups of children (n [%])

Group	n	Epileptic seizure treatment					The improvement of epileptiform discharge			
		Improved	Effectual	Going-better	Ineffective	Effective	Improved	Effectual	Ineffective	Effective
Study Group	80	57 (71.2)	10 (12.5)	7 (8.8)	6 (7.5)	74 (92.5)	45 (56.2)	23 (28.8)	12 (15.0)	68 (85.0)
Control Group	80	30 (37.5)	15 (18.8)	10 (12.5)	25 (31.2)	55 (68.8)	21 (26.3)	26 (32.5)	33 (41.8)	47 (58.8)
χ^2		—	—	—	—	14.444	—	—	—	13.635
p value		—	—	—	—	< .001	—	—	—	< .001

Note. The study group was made up of the children who received the treatment of sodium valproate combined with levetiracetam, and the control group consisted of the children who received the treatment of sodium valproate alone. "—" indicated no statistical analysis performed.

3.4 The comparison in the levels of serum S-100β and HMGB-1 between two groups of children

Before treatment, the levels of serum S-100β and HMGB-1 were compared between two groups of children, and the differences were of no statistical significance ($p > .05$). In the comparison within each group, the levels of serum S-100β and HMGB-1 after treatment were obviously lower than those before treatment, and the differences were statistically

significant ($p < .05$); after treatment, in the comparison between two groups, the levels of serum S-100β and HMGB-1 in the study group were obviously lower than those in the control group, and the differences were statistically significant ($p < .05$). See Table 4 for the comparison in the levels of serum S-100β and HMGB-1 between two groups of children.

3.5 The comparison in the rate of adverse reactions during the treatment between two groups of children

There was no significant difference between two groups in the rate of adverse reactions, such as nausea, vomiting, poor appetite, dizziness, drowsiness, hepatic and renal injury during the treatment ($p > .05$). See Table 5 for the comparison in the rate of adverse reactions during the treatment between two groups of children.

Table 3. The comparison in serum TNF-α, hs-CRP, Hcy, HCT and ESR between two groups of children ($\bar{X} \pm$ s)

Group	n	Level of serum TNF-α (pg/ml)				Level of hs-CRP (mg/L)				Level of serum Hcy (μmol/L)			
		Before Treatment	After Treatment	*t* value	*p* value	Before Treatment	After Treatment	*t* value	*p* value	Before Treatment	After Treatment	*t* value	*p* value
Study Group	80	107.9±17.8	53.1±14.0	21.644	< .001	10.1±2.5	5.0±2.5	12.902	< .001	42.2±5.8	12.5±3.1	40.393	< .001
Control Group	80	112.4±14.3	60.6±17.8	20.292	< .001	9.3±3.8	8.2±2.2	2.241	.027	41.1±2.8	15.2±3.1	55.456	< .001
t value		1.763	2.962			1.573	8.595			1.528	5.508		
p value		.080	.004			.118	< .001			.129	< .001		

Group	n	HCT (%)				ESR (mm/h)			
		Before Treatment	After Treatment	*t* value	*p* value	Before Treatment	After Treatment	*t* value	*p* value
Study Group	80	45.3±4.5	38.1±5.1	9.468	< .001	5.2±0.6	3.0±0.5	25.194	< .001
Control Group	80	44.6±5.5	40.2±3.4	3.320	.001	5.4±0.8	4.5±0.6	8.050	< .001
t value		0.881	3.064			1.789	17.178		
p value		.380	.003			.076	< .001		

Note. The study group was made up of the children who received the treatment of sodium valproate combined with levetiracetam, and the control group consisted of the children who received the treatment of sodium valproate alone. TNF-α: tumor necrosis factor-α, hs-CRP: hypersensitive C-reactive protein, Hcy: homocysteine, HCT: haematocrit, ESR: erythrocyte sedimentation rate.

Table 4. The comparison in the levels of serum S-100β and HMGB-1 between two groups of children (μg/L, $\bar{X} \pm$ s)

Group	n	Level of serum S-100β				Level of serum HMGB-1			
		Before Treatment	After Treatment	*t* value	*p* value	Before Treatment	After Treatment	*t* value	*p* value
Study Group	80	0.91±0.32	0.65±0.38	4.681	< .001	8.1±2.0	5.3±2.4	8.020	< .001
Control Group	80	0.88±0.25	0.78±0.27	2.431	.016	7.9±1.7	6.4±2.2	4.826	< .001
t value		0.661	2.495			0.842	2.840		
p value		.510	.014			.401	.005		

Note. The study group was made up of the children who received the treatment of sodium valproate combined with levetiracetam, and the control group consisted of the children who received the treatment of sodium valproate alone. HMGB-1 is high mobility group box-1.

Table 5. The comparison in the rate of adverse reactions during the treatment between two groups of children (n [%])

Group	n	Nausea & vomiting	Poor appetite	Dizziness	Drowsiness	Hepatic & renal injury	Total
Study Group	80	6 (7.5)	5 (6.2)	4 (5.0)	5 (6.2)	7 (8.8)	27 (33.7)
Control Group	80	8 (10.0)	4 (5.0)	4 (5.0)	2 (2.5)	7 (8.8)	25 (31.3)
χ^2 value		—	—	—	—	—	0.110
p value		—	—	—	—	—	.736

Note. The study group was made up of the children who received the treatment of sodium valproate combined with levetiracetam, and the control group consisted of the children who received the treatment of sodium valproate alone. "—" indicated no statistical analysis performed.

4. DISCUSSION

Children epilepsy is usually caused by paradoxical discharge of cerebral epileptogenic focus, and the course of discharge can lead to neuron damage, arousing a series of symptoms and complications, even mental retardation. It has a severe influence on children's growth and development.[8] The early standardized treatment can improve the prognosis in children with epilepsy. However, there is still a lack of effective treatment options at present. Therefore, clinically, it is urgent to look for an effective treatment option with less adverse reactions for children epilepsy.[9] It is reported in the literatures that levetiracetam has an advantage of positive effects and less adverse reactions as a novel anti-epileptic drug. The combination of levetiracetam and other anti-epileptic drugs can obviously reduce the frequency of epileptic seizure in children with epilepsy.[10] S-100β and HMGB-1 are cerebral injury factors, which can be considered as the evaluation indexes for the treatment effects of anti-epileptic drugs.[11]

The research results showed that, after treatment, the effective rates of epileptic seizure treatment and the improvement of epileptiform discharge in the study group were 92.5% (74/80) and 85.0% (68/80) respectively, which were both

significantly higher than those in the control group [68.8% (55/80) and 58.8% (47/80)]. The differences were statistically significant ($p < .05$). Before treatment, TNF-α, hs-CRP, Hcy, HCT and ESR were compared between two groups of children, and the differences were of no statistical significance ($p > .05$); in the comparison within each group, the above indicators after treatment were obviously lower than those before treatment, and the differences were statistically significant ($p < .05$); after treatment, in the comparison between two groups, the above indicators in the study group were obviously lower than those in the control group, and the differences were statistically significant ($p < .05$). It is indicated that the combination of sodium valproate and levetiracetam is better than the application of sodium valproate alone in the aspect of the curative effect, with a lower level of inflammation. It is reported in some literatures that sodium valproate is a classic anti-epileptic drug, the therapeutic mechanism of which is to improve the activity of glutamate decarboxylase (GAD) in the brain, increase the synthesis of γ-aminobutyric acid (GABA) while suppressing the degradation of GABA, enhance the reactivity of synaptosomes to GABA and restrain the paradoxical discharge of epileptogenic focus. However, it can easily lead to adverse reactions in the digestive tract;[12] levetiracetam is a novel anti-epileptic drug, and its therapeutic mechanism probably is to bind to synaptic vesicles in the brain to suppress neuron discharge in synaptosomes and hippocampal CA1 region while suppressing multiple neuronal electrical activities simultaneously in order to suppress the paradoxical discharge of epileptogenic focus, with the advantages of less adverse reactions and good curative effects. The latter can be used in combination with other anti-epileptic drugs.[3] The combination of sodium valproate and levetiracetam can acquire a satisfactory curative effect and reduce the frequency of epileptiform discharge. The research from Wu G et al.[13] shows that the combination of sodium valproate and levetiracetam has a better curative effect on the epilepsy treatment in comparison to the single use of carbamazepine, oxcarbazepine or lamotrigine. The inflammation-related indicators, including serum TNF-α, hs-CRP, Hcy, HCT and ESR, can reflect the level of inflammation in children with epilepsy. The levels of serum TNF-α, hs-CRP and other inflammatory factors are related to the degree of cerebral injury.[14] The results in this research show that the combination of sodium valproate and levetiracetam can reduce the level of inflammation in children with epilepsy. The research from Su Q and Hou X[15] shows that levetiracetam can reduce the level of inflammatory factors in the serum in children with epilepsy, which is consistent with this research.

S-100β is a type of neuroprotein, mainly existing in the cerebral neurons. It can regulate the stability of neurocytes and the rehabilitation of nerve injury. In addition, it is one of the specific markers reflecting the degree of cerebral injury and closely associated with the occurrence and prognosis of cerebral injury in children with epilepsy.[16] HMGB-1 is a protein with chromosome structure, and it exists in multiple tissue cells. It can regulate the differentiation of neurocytes and cell migration. Brain cell injury during the process of epileptic seizure can lead to the release of this protein, further aggravating the inflammatory reactions and impairing nervous tissues.[17] The research results show that, in the comparison within each group, the levels of serum S-100β and HMGB-1 after treatment are obviously lower than those before treatment, and the differences are statistically significant ($p < .05$); after treatment, in the comparison between two groups, the levels of serum S-100β and HMGB-1 in the study group were obviously lower than those in the control group, and the differences were statistically significant ($p < .05$). It is indicated that the combination of sodium valproate and levetiracetam has a greater advantage in decreasing the levels of serum S-100β and HMGB-1 during the epilepsy treatment. It is because the combination of sodium valproate and levetiracetam has a better clinical efficacy in the treatment of children epilepsy, i.e., it can significantly reduce the frequency of abnormal neuron discharge, relieve brain cell injury, decrease the levels of S-100β and HMGB-1 and then bring down the inflammatory reactions. The research from Zhang L and Cheng Y[7] indicates that the combination of sodium valproate and levetiracetam can improve the cognitive function and relieve brain cell injury in children with epilepsy during the treatment. In the case of adverse reactions, the results in this research show that there is no statistically significant difference in the rate of adverse reactions during the treatment between the study group and the control group ($p > .05$). It is indicated that the combination of sodium valproate and levetiracetam has a high safety with the accompanying adverse reactions well tolerable.

In conclusion, the efficacy of sodium valproate combined with levetiracetam is obviously better than that of sodium valproate alone in the treatment of children epilepsy. The levels of serum S-100β and HMGB-1 in children patients are more significantly reduced, resulting in a lower rate of adverse reactions, which has a certain clinical value.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

REFERENCES

[1] Ferro MA, Avery L, Fayed N, et al. Child- and parent-reported quality of life trajectories in children with epilepsy: a prospective cohort study. Epilepsia. 2017; 58(7): 1277-1286. PMid:28485850. https://doi.org/10.1111/epi.13774

[2] Auvin S. Advancing pharmacologic treatment options for pharmacologic treatment options for children with epilepsy. Expert Opin Pharmacother. 2016; 17(11): 1475-1482. PMid:27249542. https://doi.org/10.1080/14656566.2016.1195809

[3] Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: a systematic review . CNS Drugs. 2015; 29(5): 371-382. PMid:26013703. https://doi.org/10.1007/s40263-015-0248-9

[4] Meguid NA, Samir H, Bjørklund G, et al. Altered S100 calcium-binding protein B and matrix metallopeptidase 9 as biomarkers of mesial temporal lobe epilepsy with hippocampus sclerosis. J Mol Neurosci. 2018; 66(4): 482-491. PMid:30343368. https://doi.org/10.1007/s12031-018-1164-5

[5] Zhu M, Chen J, Guo H, et al. High mobility group protein b1 (HMGB1) and interleukin-1β as prognostic biomarkers of epilepsy in children. J Child Neurol. 2018; 33(14): 909-917. PMid:30303442. https://doi.org/10.1177/0883073818801654

[6] Neurology Group of Pediatric Branch of Chinese Medical Association. Expert consensus on the initial single drug therapy for the new diagnosis of epilepsy in children. Chin J Pediatr. 2015; 53(10): 734-737.

[7] Zhang L, Cheng Y. Comparison of the effects of levetiracetam and valproate on cognitive function in children with epilepsy. Med J NDFNC. 2016; 37(5): 346-347.

[8] A Yassine I, M Eldeeb W, A Gad K, et al. Cognitive functions, electroencephalographic and diffusion tensor imaging changes in children with active idiopathic epilepsy. Epilepsy Behav. 2018; 84: 135-141. PMid:29800799. https://doi.org/10.1016/j.yebeh.2018.04.024

[9] Perucca P, Scheffer IE, Kiley M. The management of epilepsy in children and adults. Med J Aust. 2018; 208(5): 226-233. PMid:29540143. https://doi.org/10.5694/mja17.00951

[10] Akter N, Rahman MM, Akhter S, et al. A randomized controlled trial of phenobarbital and levetiracetam in childhood epilepsy. Mymensingh Med J. 2018; 27(4): 776-784.

[11] Li X, Li J, Gao F, et al. Research progress of epilepsy related markers. Shandong Med J. 2018; 58(19): 108-111.

[12] Nevitt SJ, Marson AG, Weston J, et al. Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review. Cochrane Database Syst Rev. 2018; 8: CD001769. https://doi.org/10.1002/14651858.CD001769.pub4

[13] Wu G, Wu H, Xu H, et al. Comparison of the curative effects of levetiracetam and VPA used in the add-on therapy against temporal lobe epilepsy. Chin Hosp Pharm J. 2018; 38(18): 1953-1956.

[14] Chen WZ, Tan Y, Ge YX, et al. The effects of levetiracetam on cerebrospinal fluid and plasma NPY and GAL, and on the components of stress response system, hs-CRP, and S100B protein in serum of patients with refractory epilepsy. Cell Biochem Biophys. 2015; 73(2): 489-494. PMid:27352343. https://doi.org/10.1007/s12013-015-0683-8

[15] Su Q, Hou X. Influence of levetiracetam on the serum cytokines and cognitive state related indexes of patients with epilepsy. Hainan Med J. 2017; 28(22): 3648-3651.

[16] Asadollahi M, Simani L. The diagnostic value of serum UCHL-1 and S100-B levels in differentiate epileptic seizures from psychogenic attacks. Brain Res. 2019; 1704: 11-15. PMid:30253122. https://doi.org/10.1016/j.brainres.2018.09.028

[17] Liu AH, Wu YT, Wang YP. MicroRNA-129-5p inhibits the development of autoimmune encephalomyelitis-related epilepsy by targeting HMGB1 through the TLR4/NF-κB signaling pathway. Brain Res Bull. 2017; 132: 139-149. PMid:28528202. https://doi.org/10.1016/j.brainresbull.2017.05.004