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Original Article

Clinical efficacy and safety of the combined use of sodium valproate and levetiracetam in epilepsy children

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Abstract: Objective: To explore the clinical efficacy and safety of the combined use of sodium valproate (VPA) and levetiracetam in epilepsy children. Methods: 108 children with epilepsy admitted to our hospital were categorized to receive levetiracetam alone (n = 54, group A) or leveritacetam with VPA (n = 54, group B). The overall clinical characteristics and serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), phosphorus, and calcium were determined before and after treatment for comparisons between the two groups. Results: Obvious decrease in serum TNF-α and IL-6 levels in two groups were detected after treatment; group A exhibited much higher levels than group B ($P < 0.001$). Similarly, there were significant reductions both in the serum phosphorus and in the calcium levels in groups A and B following treatment. Importantly, these levels in group A were obviously higher than those in B ($P < 0.001$). Compared to group A, group B exhibited better electroencephalogram outcomes, and the difference in overall improvement rate (OIR) between two groups is statistically significant ($P < 0.05$). The incidence of adverse reactions was notably higher in group A than in group B ($P < 0.05$). Conclusion: The combined use of Levetiracetam and VPA could decrease inflammatory response and multiple organ impairment, and ameliorate bone metabolism of epilepsy children; It also shows better safety profile and worth recommendation for more clinical applications.

Keywords: Epilepsy, sodium valproate, levetiracetam, clinical efficacy

Introduction

Epilepsy is a common neurology encephalopathy with an incidence that is more than ten-fold higher in children compared with adults [1, 2]. Pediatric epilepsy, a brain dysfunction syndrome, is associated with serious injury to cranial nerves and poses great physical and psychological burden to patients and their families [3, 4]. Treatment options for pediatric epilepsy are limited due to safety issues, given that development in children is not complete and the drug metabolizing ability of children is less potent than that of adults [5]. Therefore, an important approach in pediatric epilepsy is to provide treatments that are more appropriate for children [6].

The existing broad-spectrum antiepileptic drugs, levetiracetam and, sodium valproate (VPA), are usually used for pediatric epilepsy (PE) treatment [7]. However, the overall clinical efficacy of monotherapy with VPA or levetiracetam alone in children with epilepsy is unsatisfactory, with an extremely high epilepsy recurrence due to a weak immune system in children [8, 9]. Studies demonstrated that the effects of broad-spectrum antiepileptics on bone metabolism and inflammatory response in children varied among antiepileptic drugs. Therefore, choosing appropriate treatments are clinically important to improve bone metabolism and alleviate inflammatory response [10, 11]. Nevertheless, almost no studies were conducted to investigate the safety and efficacy of the combined use of VPA and levetiracetam in PE treatment. We therefore performed such study to evaluate the safety of this combined treatment and to analyze the difference in efficacy among distinct treatment schemes on bone metabolism indicators, such as serum phosphorus and calcium levels in epilepsy children.

Materials and methods

General data

Form 2016 to 2019, a total of 108 epilepsy children was enrolled in the Zhongxiang Hospital of

Renmin Hospital of Wuhan University diagnosis criteria [12] were categorized to receive levetiracetam alone (group A) or in combination with VPA (group B). The inclusion criteria: 1) There are two or more unprovoked seizures within a time interval of ≥ 24 hours; 2) One unprovoked seizure, which meets the established criteria for epilepsy syndrome, or has a risk of epilepsy recurrence ≥ 60%. The exclusion criteria included severe liver or kidney dysfunction, coagulopathy, lack of willingness to follow examinations and study procedures, and cognitive and communication impairment. There were 34 males and 20 females in group A (n = 54), with a mean age of 9.12 ± 1.04 years, whereas there were 35 males and 19 females in group B (n = 54), with a mean age of 8.93 ± 2.05 years.

All patients and their families agreed to participate in the experiment and signed the informed consent form. The study has been approved by the Ethics Committee of Renmin Hospital of Wuhan University.

Treatment plan

Children in group A were treated only with oral levetiracetam (UCB Pharma, Belgium; National Medicine Permission No. J20160085), at an initial dose of 10 mg/kg/day for 7 d; the dose would be adjusted to 10-40 mg/kg/day if no obvious efficacy was detected.

Children in group B were treated with levetiracetam plus VPA. The treatment plan for levetiracetam was the same as that in group A. The initial dose for oral VPA (Sanofi Pharmaceutical, Hangzhou; National Medicine Permission No. H20010595) was 15-60 mg/kg/day for one week; the dose based on the original drug concentration was increased to 5-10 mg/kg/d if the treatment effect was not significant. All children in both groups were treated for four weeks.

Outcome measurements

The clinical data and parameters in two groups during pre- and post treatment were analyzed: serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), phosphorus, and calcium. In addition, adverse reactions including nausea, vomiting, somnolence, gastrointestinal discomfort, and abnormal liver function were compared between the groups. The improvement and response rates were based on electroencephalogram findings. The rate of overall improvement was calculated as follows: overall improvement = (controlled + significantly improved + improved patient numbers)/total patient number × 100%, and clinical efficacy [13] was calculated as follows: overall response rate = (number of patients controlled + significant response + response)/total patients × 100%.

Measurement of serum parameters

Peripheral venous blood was collected using sodium citrate-containing vacuum blood collection tubes before and 7 days after treatment. All blood samples were centrifuged at 3500 rpm at 4°C for 15 min within 3 h after collection. Serum was collected and preserved at -80°C until use.

The levels of TNF-α and IL-6 were determined by enzyme-linked immunosorbent assay, and all procedures were performed per the manufacturers' instructions. Briefly, 100 μl standard solution, patient serum samples, and negative and positive controls were added into wells, and 100 μl antibody solution was added to each well. The wells were covered with sealing film, mixed, and incubated for 40 min. Next, 100 μl streptavidin solution was added to each well, followed by mixing and incubation for 40 min. After the removal of the contents, the wells were washed five times with washing buffer by shaking slowly for 1 min each. Next, 100 μl substrate A solution and 100 μl substrate B solution were added to each well and incubated for 5 min, with protection from light after sealing. Next, 100 μl stop solution was added to each well, and a microplate reader was used to read optical density at a wavelength of 450 nm. The levels of TNF-α and IL-6 were calculated eventually.

Serum calcium and blood phosphorus were determined through an automatic biochemical analyzer.

Statistical methods

SPSS software version 19.0 (Bizinsight Infor-Tech, Beijing) was used for statistical analysis of the data obtained in the current study. Enumeration data were investigated through chi-square test. The data obtained were expressed as average ± SD and compared by

Table 1. General clinical characteristics of the treatment groups

Parameters	Group A (n = 54)	Group B (n = 54)	t/X^2	*P*
Sex			0.040	0.841
M	34 (62.96)	35 (64.81)		
F	20 (37.04)	19 (35.19)		
Body weight (kg)	31.57 ± 2.06	31.29 ± 1.49	0.393	0.695
Mean age (years)	9.12 ± 1.04	8.93 ± 2.05	0.809	0.420
Obesity			1.363	0.243
Yes	28 (51.85)	34 (62.96)		
No	26 (48.15)	20 (37.04)		
High-salt diet			0.152	0.697
Yes	30 (55.55)	32 (59.26)		
No	24 (44.44)	22 (40.74)		
Vitamin deficiency			7.636	0.006
Yes	40 (74.07)	26 (48.14)		
No	14 (25.93)	28 (51.85)		
Family history of epilepsy			1.174	0.279
Yes	10 (18.52)	6 (11.11)		
No	44 (81.48)	48 (88.89)		
History of perinatal brain injury			0.624	0.430
Yes	23 (42.59)	19 (36.19)		
No	31 (57.41)	35 (64.81)		

multifactor analysis. GraphPad Prism 6 software was used for plotting figures. A *P* value < 0.05 was defined to indicate statistical significance.

Results

The clinical characteristics of the study cohort

As shown in **Table 1**, the overall clinical characteristics were not significantly different between the two groups (*P* > 0.05).

Changes in serum TNF-α and IL-6 levels with treatment

The serum TNF-α levels during pre- and post-treatment were 16.82 ± 2.13 and 7.39 ± 1.69 pg/ml in group A and 16.09 ± 2.55 and 4.20 ± 1.76 pg/ml in group B, respectively. After treatment, the serum levels of TNF-α were reduced significantly in both groups; besides, the levels in group B were noticeably lower over those in group A (*P* < 0.001) (**Figure 1A**).

The serum levels of IL-6 before and after treatment were 50.63 ± 2.81 and 38.29 ± 2.45 ng/l in group A and 50.43 ± 2.37 and 26.20 ± 2.49 ng/l in group B, respectively. Whereas no obvious distinction in the serum IL-6 levels prior treatment was detected (*P* > 0.05), the serum IL-6 levels after treatment were reduced significantly in both groups. To be important, the serum IL-6 levels in group B were dramatically lower over those in group A following treatment (*P* < 0.001) (**Figure 1B**).

Changes in serum phosphorus and calcium levels after treatment

We analyzed changes in serum phosphorus levels of two groups after treatment. The serum phosphorus levels during pre- and post-treatment were 2.53 ± 0.63 and 2.20 ± 0.43 mmol/l in group A and 2.54 ± 0.61 and 1.23 ± 0.55 mmol/l in group B, respectively. No obvious distinction in serum phosphorus levels of two groups prior to treatment was detected (*P* > 0.05). Following treatment, the serum phosphorus levels were dramatically decreased in two groups, and group A exhibited a much higher level (*P* < 0.001) (**Table 2**).

The serum levels calcium before and after treatment were 1.62 ± 0.31 and 1.39 ± 0.28 mmol/l in group A and 1.61 ± 0.28 and 1.10 ± 0.17 mmol/l in group B, respectively. No obvious distinction in the serum calcium levels of two groups prior to treatment were detected (*P*

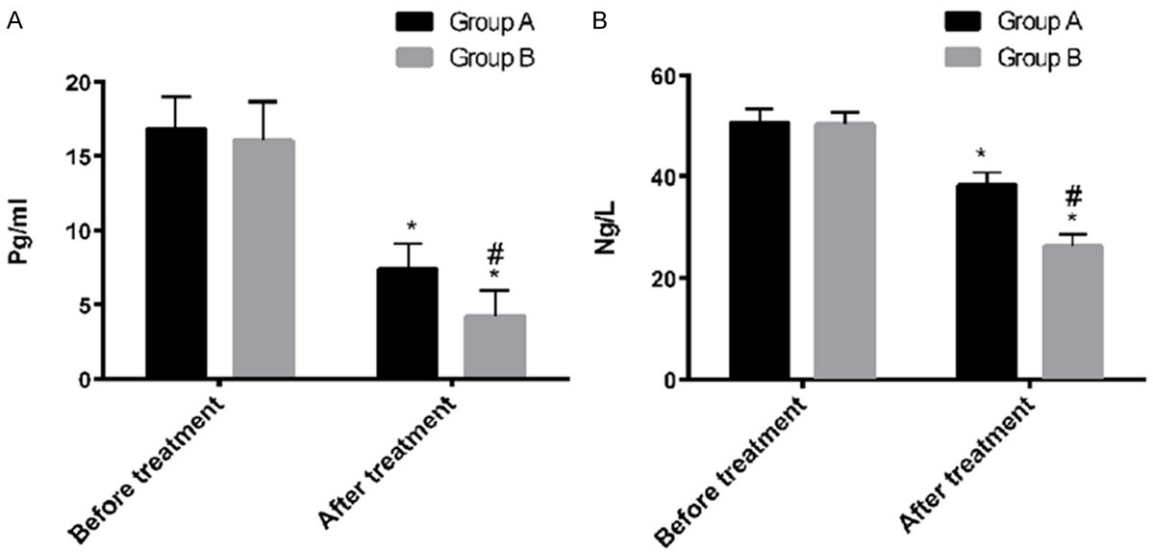

Figure 1. Changes in TNF-α and Il-6 levels in groups A and B after treatment. A. *Obvious decrease in TNF-α levels in two groups after treatment. #Significant difference in TNF-α level in group B compared with group A after treatment ($P < 0.001$). B. *Significant reduction in IL-6 levels in both groups with treatment. #Significant difference in IL-6 level in group B compared with group A after treatment ($P < 0.001$).

Table 2. Serum phosphorus levels before and after treatment in groups A and B

	Group A (n = 54)	Group B (n = 54)	t	*P*
Before treatment (mmol/L)	2.53 ± 0.63	2.54 ± 0.61	0.084	0.933
After treatment (mmol/L)	2.20 ± 0.43	1.23 ± 0.55	10.210	< 0.001
t	3.179	8.025		
P	< 0.001	< 0.001		

Table 3. Serum calcium levels before and after treatment in groups A and B

	Group A (n = 54)	Group B (n = 54)	t	P
Before treatment (mmol/L)	1.62 ± 0.31	1.61 ± 0.28	0.861	0.176
After treatment (mmol/L)	1.39 ± 0.28	1.10 ± 0.17	6.506	< 0.001
t	4.551	7.036		
P	< 0.001	< 0.001		

Table 4. Comparison of clinical efficacy between groups A and B

	Group A (n = 54)	Group B (n = 54)	X^2	*P*
Controlled	14 (25.93)	20 (37.04)	-	-
Significant improvement	8 (14.81)	10 (18.52)	-	-
Improvement	5 (9.26)	8 (14.81)	-	-
No improvement	27 (50.00)	16 (29.63)	-	-
Rate of overall improvement	27 (50.00)	38 (70.37)	4.675	0.031

> 0.05). Following treatment, the serum calcium levels were dramatically decrease in two groups, and group A exhibited a much higher level ($P < 0.001$) (**Table 3**).

Comparison of the clinical efficacy between the treatment groups

Comparison of the electroencephalogram findings between the two groups revealed that 5, 14, 5, and 27 patients in group A exhibited disease control, significant improvement, improvement, and ineffective treatment, respectively. Conversely, 20, 10, 8, and 16 patients in group B exhibited disease control, significant improvement, improvement, and ineffective treatment, respectively. Group B, in relation to A exhibited better electroencephalogram results, with a obvious distinction in the OIR of two groups ($P < 0.05$) (**Table 4**).

Table 5. Comparison of clinical efficacy between groups A and B

	Group A (n = 54)	Group B (n = 54)	X^2	*P*
Controlled	12 (22.22)	15 (27.78)	-	-
Significant response	10 (18.52)	10 (18.52)	-	-
Response	12 (22.22)	11 (20.37)	-	-
No response	20 (37.04)	18 (33.33)	-	-
Overall response rate	34 (62.96)	36 (66.67)	0.162	0.687

Table 6. Comparison of adverse reactions between groups A and B

Groups	Group A (n = 54)	Group B (n = 54)	X^2	*P*
Nausea	2 (3.70)	0 (0.00)	-	-
Vomiting	1 (1.85)	0 (0.00)	-	-
Drowsiness	1 (1.85)	0 (0.00)	-	-
Gastrointestinal discomfort	2 (3.70)	1 (1.85)	-	-
Liver dysfunction	2 (3.70)	1 (1.85)	-	-
Overall incidence	8 (14.81)	2 (3.70)	3.967	0.046

Comparison of the two groups for therapeutic effect of the two treatment approaches revealed that there were 12, 10, 12, and 20 patients exhibiting control, significant response, response, and no response, respectively, in group A. Conversely, 15, 10, 11, and 18 patients had control, significant response, response, and no response, respectively, in group B. The overall response rates in two groups exhibited no obvious distinction ($P > 0.05$) (**Table 5**).

Differences in adverse reactions between two groups

The incidence of adverse reactions, like nausea, vomiting, somnolence, gastrointestinal discomfort, and abnormal liver function in group B were dramatically lower over that in group A ($P < 0.05$) (**Table 6**).

Discussion

In this study, we evaluated the clinical safety, efficacy and inflammation status in epilepsy children treated with levetiracetam alone or together with VPA. The findings showed that the serum TNF-α and IL-6 levels, which exhibited obvious difference in two groups prior to treatment, were noticeably decreased after treatment. Additionally, group A exhibited much higher levels. Several pathological studies demonstrated massive proliferation of glial cells in brain tissue specimens of children with epilepsy, suggesting that the development and progression of epilepsy are often accompanied by an increase in inflammatory response [3, 14]. Similar studies demonstrated that levetiracetam decreased the expression of inflammatory factors in cerebrospinal fluid or serum of epilepsy patients [15]. Studies also found that sufficient TNF-α secretion plays a protective role, whereas excessive TNF-α production might indirectly induce local inflammatory response and organ damage [16, 17]. Expression of IL-6 in the blood of patients with epilepsy is much higher than that in normal individuals [18, 19]. On this basis, it is speculated in our study that the down-regulatory effect of VPA combined with levetiracetam on related inflammatory factors of TNF-α and IL-6 in children with epilepsy should be better than levetiracetam alone and consequently may better relieve the inflammatory response in these children.

In the current study, we further compared changes in serum phosphorus and calcium levels in children treated with levetiracetam alone and those treated with VPA plus levetiracetam. We observed that the serum phosphorus and calcium levels were decreased in two groups and that this effect was more prominent in the patients treated with VPA and levetiracetam. Antiepileptic drugs abuse usually resulted in bone metabolism dysfunction in epilepsy children. Serum phosphorus and calcium levels, as common clinical indicators for bone metabolism, have an important predictive value for changes in bone metabolism in these patients [20, 21]. Hence, the study displayed that the combined use of VPA and levetiracetam can cause the more prominent decrease in serum phosphorus and calcium levels, thereby better ameliorating bone metabolism in epilepsy children.

Finally, we assessed the electroencephalogram findings for therapeutic effect and overall adverse effects by comparing VPA in combination with levetiracetam to levetiracetam alone in children with epilepsy. We observed that no

obvious difference existed in clinical efficacy of two groups; however, assessment by electroencephalogram revealed that the improvement was significantly better in those with the combination treatment.

In contrast, the incidence of adverse reactions were dramatically lower in epilepsy children treated with VPA plus levetiracetam. Relevant studies revealed that levetiracetam assumed a critical part in treating PE with a favorable safety profile and that it was excreted normally through kidneys. Apparently, the combined use of levetiracetam and VPA may considerably ameliorate clinical efficacy in epilepsy children [22, 23]. Hence, the study displayed that the combined use of VPA and levetiracetam leads to less adverse effect, such as less nausea, vomiting, drowsiness, Gastrointestinal, discomfort, Liver dysfunction,overall incidence.

There are several limitations in the current study. First, the therapeutic effect of different drug doses was not evaluated, and the insufficient sample size may lead to deviations in our conclusions. In addition, few studies reported on the effects of VPA in combination with levetiracetam on bone metabolism, and future studies are required to validate the conclusions of the current study.

In summary, in children with epilepsy, levetiracetam in combination with VPA might reduce damage to various organs and dampen inflammatory response while improving bone metabolism as a treatment approach with better safety profile. Therefore, levetiracetam in combination with VPA should be recommended for more clinical applications.

Disclosure of conflict of interest

None.

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