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Observation of the efficacy of naloxone combined with acyclovir in the treatment of children viral encephalitis and its impacts on IL-1 and IL-6

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Abstract. – OBJECTIVE: To analyze the clinical efficacy of naloxone combined with acyclovir in the treatment of children viral encephalitis and the impacts on inflammatory factors IL-1 and IL-6.

PATIENTS AND METHODS: 96 children with viral encephalitis were retrospectively analyzed. They were treated from July 2013 to January 2014 in our hospital. They were divided into control group (45 cases treated with acyclovir) and observation group (51 cases treated with acyclovir combined with naloxone). Both groups were treated with comprehensive measures. Changes of the content of serum IL-1 and IL-6 in the two groups before and after treatment were monitored by enzyme-linked immunosorbent assay (ELISA). Signs, recovery time of clinical symptoms, total effective rate, occurrence of adverse reactions and adverse reactions after treatment of children in the two groups were compared.

RESULTS: Levels of serum IL-1 and IL-6 of children in the control group and the observation group decreased after treatment, and the decrease was greater in the observation group ($p<0.05$). Signs and recovery time of clinical symptoms of the observation group were significantly shorter than that of the control group ($p<0.05$). Indexes of serum in the observation group were significantly lower than those of the control group after treatment ($p<0.05$). The total effective rate of the observation group was significantly higher than that of the control group ($p<0.05$). The prevalence of adverse reactions and sequelae in the observation group were lower than those in the control group ($p<0.05$).

CONCLUSIONS: In the treatment of children, viral encephalitis has naloxone combined with ganciclovir had a more significant effect on the decrease of levels of serum IL-1 and IL-6; naloxone combined with acyclovir in the treatment of children viral encephalitis had better effects, lower adverse reactions and lower prevalence of sequelae compared with sole medication, which is worth clinical promotion.

Key Words:
Children viral encephalitis, Naloxone, Acyclovir, IL-1, IL-6.

Introduction

Encephalitis is a serious neurological disease with inflammation in the brain parenchyma. More than 100 infectious, postinfectious and immune-mediated diseases could cause encephalitis. The most common encephalitis is viral encephalitis. The etiology of sequelae and mortality caused by viral encephalitis are 7.5% and 0.8%, respectively[1]. Infection accounts for about 50% of identifiable cases and is the most common etiological type of encephalitis[2]. Encephalitis is characterized by fever, neurological deficits, epilepsy, cytosis, neuroimaging and EEG abnormalities[3]. It is estimated that herpes simplex virus encephalitis is the most important treatable viral enceph-

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alitis with an incidence of about one in every million cases per year. About 2,000 cases occur each year in the United States. About 90% herpes simplex virus encephalitis cases are caused by herpes simplex virus[4]. Therefore, timely identification of encephalitis and timely treatment could save lives. Clinicians should be able to identify the clinical signs and symptoms of infection and be familiar with reasonable diagnostic methods and treatments. Early identification and treatment are key to improving outcomes[5].

Naloxone is a potent opioid antagonist that has strong effects on the μ opioid receptor. It is approved by the FDA for emergency treatment of known or suspected opioids overdose with respiratory or central nervous system depression. Naloxone could be administered intravenously (IV), intramuscularly (IM), subcutaneously (SC) and intranasally (IN)[6]. Naloxone has fast onset, strong affinity, and good safety. Several studies[7,8] have shown that it has a good effect in the treatment of viral encephalitis in children. In many studies[9], it has been regarded as one of the first-class therapeutic drugs for viral encephalitis in children. However, with the development of the disease in recent years, some scholars[10] have shown that long-term, large-dose use of naloxone may cause arrhythmia, pulmonary edema and even myocardial infarction in children. Therefore, there is an extremely urgent clinical need to find a new alternative to naloxone or reduce the side effects of naloxone for the treatment of viral encephalitis in children. Acyclovir is a antivirus agent in nucleotide that has antiviral activity against herpes virus (a member of DNA virus) *in vitro*. Effects of acyclovir treatment are maximized by early initiation of treatment, especially in non-primary infection. It tends to have fewer extended treatments than the initial episode. The mechanism of acyclovir includes: 0,1 Highly selective inhibition of DNA replication in herpes virus. 0,2 Enhancing the uptake of herpes infected nerve cells and phosphorylation of herpes virus thymidine kinase. 0,3 The substrate specialization of acyclovir triphosphate on viral rather than cellular DNA polymerase[11]. The IL-1 cytokine family comprises 11 members (7 ligands with agonistic activity, 3 receptor antagonists and 1 anti-inflammatory cytokine). IL-1 targeted therapy has been successfully used to treat a range of inflammatory conditions[12]. Interleukin-6 (IL-6) is a pleiotropic four-helix bundle cytokine that performs many functions *in vivo*[13]. Several cytokines play roles in the inflammatory response, one of which is interleukin-6 (IL-6). IL-6 is released as a response to tissue damage or inflammatory stimuli, producing physiological responses as needed. The concentration of IL-6 increases in post-traumatic and chronic diseases. IL-6 acts as a pro-inflammatory mediator and an anti-inflammatory modulator that stimulates potent anti-inflammatory cytokines[14]. IL-6 is an inflammatory cytokine with a wide range of biological effects. Neuroinflammation has been widely demonstrated to play a key role in the development of pathological pain[15].

The aim of this study was to investigate the efficacy of naloxone combined with acyclovir in the treatment of children viral encephalitis, as well as the effects on interleukin IL-1 and IL-6, providing an accurate reference for future clinical treatment of children viral encephalitis.

Patients and Methods

General Materials

96 children with viral encephalitis were retrospectively analyzed in this study. They were admitted to our hospital from July 2013 to January 2014. Among them, there were 55 males, with an age of (2.87±2.54), and the average course of disease was (3.35±0.57) days. There were 41 females with an age of (2.67±2.48), and the average course of disease was (3.22±0.53) days. According to different treatment methods, 51 cases were divided into the observation group and 45 cases were divided into the control group. Comprehensive treatments were performed in both groups. The observation group was treated with acyclovir combined with naloxone on the premise of comprehensive treatments, and the control group was only treated with acyclovir alone. This study has been approved by the Ethics Committee of Zouping People's Hospital, and families of all the above children have signed the informed consent.

Inclusion and Exclusion Criteria

All children met clinical practice guidelines for medical-related ventriculitis and meningitis of the 2017 American Society of Infectious Diseases[16]. The exclusion criteria were as follows: children with severe cardiovascular disease and other serious diseases, drug allergies, liver and kidney dysfunction, central nervous system organic disease.

Methods

All children were given conventional treatments, such as oxygen uptake, reduction in intracranial pressure, maintenance of water and electrolyte balance, antipyretic, antiviral therapy, etc. The control group was given acyclovir injection (acyclovir injection, Yantai Zhichu Pharmaceutical Co., Ltd., SFDA Approval No. H20052414) on the basis of conventional treatment. Acyclovir was diluted to at least 100 ml with 0.9% normal saline or 5% dextrose water, so that the concentration of the final drug was less than 7 g/L, with the dosage of 10 mg / (kg · d);

The observation group employed acyclovir injection combined with naloxone on the basis of conventional treatment (naloxone hydrochloride injection, Beijing Sihuan Pharmaceutical Co., Ltd., SFDA Approval No. H20055758). Naloxone 0.01-0.03 mg/(kg · times) was intravenously dripped once every 8 hours and diluted with 10 ml glucose (10% concentration). Both groups were treated for one week.

The Efficacy Criteria and Observation Indicators

Markedly effective: the body temperature of children returned to normal within 3 days of treatment. The clinical symptoms, such as vomiting, convulsion, headache and disturbance of consciousness were reduced, and the signs were stable. Effective: the body temperature of children returned to normal within 5 to 7 days. The clinical symptoms, such as vomiting, convulsion, headache and disturbance of consciousness disappeared, and signs were stable. Ineffective: after 7 days of treatment, clinical symptoms and signs such as fever, vomiting, convulsion, headache, and disturbance of consciousness were not eliminated. During the treatment, 5 ml of venous blood were extracted from all children on an empty stomach. The levels of serum IL-1 and IL-6 were measured by ELISA. The IL-1 test kit was purchased from Shanghai Shumai Biotechnology Co., Ltd. (article number CM-0179H1); the IL-6 test kit was purchased from Shanghai Chunshi Biotechnology Co., Ltd. (article number CS-13629E). The operation was in strict accordance with the instructions of kit.

Statistical Analysis

SPSS 24.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY, USA) software analysis was used to perform statistical analysis of all collected results. The measurement data were measured by mean plus standard error (x±s), and *t*-test was employed. Multiple time points were measured by repeated measures analysis of variance and Bonferroni back testing. The counting data was expressed as a percentage, using the χ^2-test. The data were statistically significant when $p<0.05$.

Results

General Meterials of Children

As shown in Table I, the two groups of children were comparable in terms of general materials and there was no significant difference.

Comparison of Clinical Effects of Children Between the Two Groups

The total effective rate of the observation group was 96.1%, which was significantly higher than that of the control group (82.2%). As shown in Table II, the difference between the two groups was statistically significant ($p<0. 05$).

Adverse Reactions and Sequelae of Children in the Two Groups

The adverse reactions and sequelae were compared between the two groups after treatment. The results showed that the observation group was significantly better than the treatment group, and differences between the two groups were statistically significant ($p<0.05$), as shown in Table III.

Comparison of Concentrations of IL-1 and IL-6 in Different Clinical Pathological Features

Concentration changes of IL-1 and IL-6 in different pathological features were observed. There was no difference in the concentration of IL-1 in different clinical features such as different age, gender, course of disease, nationality and place of residence ($p>0.05$), as shown in Table IV. There was no difference in the concentration of IL-6 in clinical features, such as age, gender, course of disease, nationality and place of residence ($p>0.05$), as shown in Table V.

Comparison of Serum Indexes

Changes of levels of IL-1 and IL-6 in the four different time periods were observed before and after treatment. Levels of IL-1 at T1 and T2 were compared ($p>0.05$). Levels of IL-1 in the two groups were significantly different from those at

Table I. General materials of children with viral encephalitis in the two groups.

	Observation group (n = 51)	Control group (n = 45)	χ^2 or t	p
Gender			0.064	0.800
Male	33 (64.7)	28 (62.2)		
Female	18 (35.3)	17 (37.8)		
Age (year)			0.134	0.893
	2.83 ± 2.57	2.76 ± 2.52		
Weight (kg)			0.299	0.766
	12.57 ± 3.83	12.34 ± 3.67		
Height (cm)			0.547	0.586
	91.23 ± 9.88	92.33 ± 9.79		
Course of disease			0.637	0.526
	3.33 ± 0.56	3.26 ± 0.51		
Place of residence			0.567	0.451
City	40 (78.4)	38 (84.4)		
Country	11 (21.6)	7 (15.6)		
Nationality			0.228	0.633
Han	49 (96.0)	44 (97.8)		
Minority	2 (3.9)	1 (2.2)		
Smoking history of parents			0.032	0.858
Yes	27 (52.9)	23 (51.1)		
No	24 (47.1)	22 (48.9)		
Drinking history of parents			0.256	0.613
Yes	35 (68.6)	33 (73.3)		
No	16 (31.4)	12 (26.7)		
Genetic disease history of parents			0.100	0.752
Yes	3 (5.9)	2 (4.4)		
No	48 (94.1)	43 (95.6)		
Way of birth			0.024	0.878
Eutocia	46 (90.2)	41 (91.1)		
Cesarean	5 (9.8)	4 (8.9)		

Table II. Clinical effects of children in the two groups.

Groups	Markedly effective	Effective	Ineffective	Total effective rate	χ^2	p
Observation group (n = 51)	18 (0.353)	31 (0.608)	2 (0.039)	49 (0.961)	4.919	0.027
Control group (n= 45)	16 (0.356)	21 (0.467)	8 (0.178)	37 (0.822)		

T3 and T4 before treatment (p<0.05), as shown in Table VI. Levels of IL-1 in the four different time periods between the two groups were compared (p<0.05), as shown in Figure 1. Levels of IL-6 at T1 and T2 were compared (p>0.05). Levels of IL-6 at T3 and T4 were significantly different compared with those before treatment (p<0.05), as shown in Table VII. Levels of IL-6

Table III. Adverse reactions and sequelae of children after treatment in two groups.

	Observation group (51)	Control group (45)	χ^2	p
Headache	13 (25.5)	22 (48.9)	5.650	0.018
Disturbance of consciousness	8 (15.7)	15 (33.3)	4.086	0.043
Nausea	4 (7.8)	11 (24.4)	4.998	0.025
Vomiting	2 (3.9)	9 (20.0)	5.922	0.015
Drowsiness	3 (5.9)	11 (24.4)	6.613	0.010
Epilepsy	1 (1.9)	6 (13.3)	4.574	0.033
Convulsion	2 (3.9)	12 (26.7)	9.929	0.001
Total	33	86	37.45	< 0.01

Table IV. Concentration changes of IL-1 in different pathologies.

	N	IL-1	*t* or F	*p*
Age (year)			0.196	0.845
> 3	47	1.83 ± 0.51		
≤ 3	49	1.85 ± 0.49		
Gender			0.163	0.870
Male	55	1.84 ± 0.61		
Female	41	1.86 ± 0.57		
Course of disease (d)			0.347	0.729
> 4	38	1.85 ± 0.45		
≤ 4	58	1.82 ± 0.39		
Nationality			0.186	0.853
Han	83	1.84 ± 0.35		
Minority	13	1.86 ± 0.43		
Place of residence			0.364	0.717
City	61	1.83 ± 0.45		
Country	47	1.86 ± 0.39		

in the four different time periods between the two groups were compared ($p<0.05$), as shown in Figure 2.

Correlation Between IL-1, IL-6 and the Time of Treatment

Correlation analysis showed that IL-1 and IL-6 were negatively correlated with the time of treatment (r=-0.657, -0.545, $p<0.050$), as shown in Figure 3, Figure 4 and Table VIII.

Discussion

Viral infections in the central nervous system are the main cause of encephalitis[17]. Viral encephalitis causes acute inflammation of the brain parenchyma and is an important cause of human morbidity and mortality. Although herpes simplex encephalitis is the most common cause of fatal sporadic encephalitis in human[18], this disease is a potentially fatal infectious disease with high morbidity and mortality. With regard to in-hospital mortality in newborns, children and adults were respectively 6.9%, 1.2%, and 7.7%[19]. Since the immune system in childhood is weaker than that of adults, the virus easily invades the nervous system and causes viral encephalitis. At present, viral encephalitis is becoming more and more frequent in clinic and the disease is more and more complicated. It is a research hotspot to seek safe, fast and effective treatment. With the development of viral encephalitis, the deficiencies of naloxone's efficacy have been gradually

Table V. Concentration changes of IL-6 in different pathological features.

	N	IL-6	*t* or F	*p*
Age (year)			0.288	0.774
> 3	47	108.65 ± 10.34		
≤ 3	49	109.24 ± 9.75		
Gender			0.854	0.396
Male	55	110.54 ± 8.79		
Female	41	108.94 ± 9.47		
Course of disease (d)			1.027	0.307
> 4	38	111.57 ± 8.93		
≤ 4	58	109.64 ± 9.05		
Nationality			0.183	0.855
Han	83	108.43 ± 10.32		
Minority	13	107.86 ± 11.12		
Place of residence			0.715	0.476
City	61	110.34 ± 9.12		
Country	47	108.91 ± 11.66		

Table VI. Concentration changes of IL-6 in different pathological features.

	Observation group	Control group
T1	5.37 ± 2.14	5.41 ± 2.16
T2	4.41 ± 1.89[a]	4.57 ± 1.91[d]
T3	3.23 ± 1.02[ab]	4.26 ± 1.42[de]
T4	2.12 ± 0.45[abc]	3.17 ± 1.03[def]
F	43.41	13.55
p	< 0.001	< 0.001

Note: [a]Indicated that the same groups were compared with T1, [a]$p<0.05$, b indicated that the same groups were compared with T2, [b]$p<0.05$, c indicated that the same groups were compared with T3, [c]$p<0.05$; d indicated that the same control groups were compared with T1, [d]$p<0.05$, e indicated that the same control groups were compared with T2, [e]$p<0.05$, f indicated that the same control groups were compared with T3, [f]$p<0.05$.

Table VII. Changes in IL-6 levels during treatment.

	Observation group	Control group
T1	134.53 ± 24.10	134.78 ± 23.91
T2	128.73 ± 19.31[a]	127.34 ± 20.13[d]
T3	115.65 ± 15.27[ab]	123.57 ± 17.13[de]
T4	108.73 ± 9.8[abc]	118.62 ± 13.16[de]f
F	22.18	5.787
p	< 0.001	< 0.001

Note: [a]Indicated that the same groups were compared with T1, [a]$p<0.05$, b indicated that the same groups were compared with T2, [b]$p<0.05$, c indicated that the same groups were compared with T3, [c]$p<0.05$; d indicated that the same control groups were compared with T1, [d]$p<0.05$, e indicated that the same control groups were compared with T2, [e]$p<0.05$, f indicated that the same control groups were compared with T3, [f]$p<0.05$.

revealed. Therefore, effective intervention is the key to improving the rehabilitation of children with viral encephalitis.

For the treatment of viral encephalitis, naloxone is a synthetic oxymorphone N-allyl derivative. It is an effective drug for reversing cardiovascular and respiratory depression associated with anesthesia, and sometimes may bring non-narcotic overdose. It is essentially a pure anesthetic antagonist, relatively safe, and a useful diagnostic and therapeutic agent for the treatment of brain diseases[20]. Herpes simplex virus encephalitis is a life-threatening complication of herpes simplex virus infection. Acyclovir is the preferred antiviral treatment[21]. Acyclovir is the first line treatment for herpes virus infection and requires activation by phosphorylation as a form of triphosphate. Initially, phosphorylation occurs through the thymidine kinase encoded by the human herpesvirus 1 UL23 gene. Further phosphorylation occurs through cellular thymidylate kinase. Activated trimethylol phosphate is a competitive inhibitor of viral DNA polymerase and leads to chain termination[22]. In recent years,

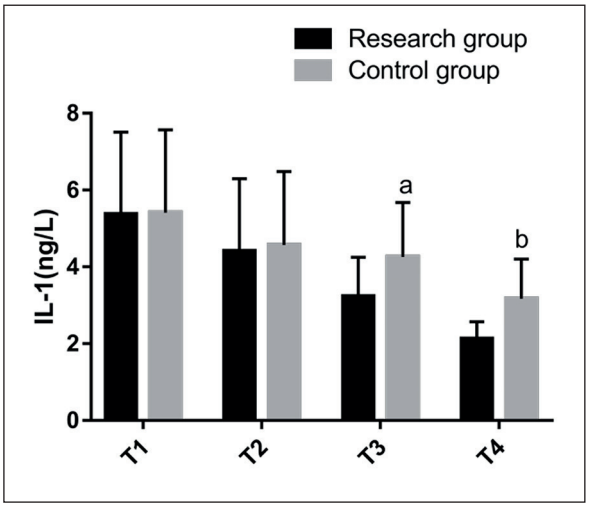

Figure 1. IL-1 levels of patients between the two groups before and after treatment were compared. There was no significant difference in IL-1 levels between the two groups before and after treatment ($p>0.05$); a represented the IL-1 level compared with the observation group at T3, $p<0.05$; b represented the IL-1 level compared with the observation group at T4, $p<0.05$.

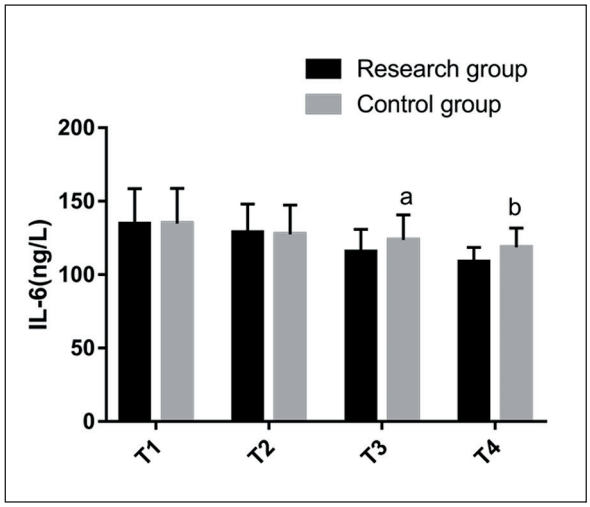

Figure 2. IL-6 levels of patients in the four different time periods between the two groups before and after treatment were compared. There was no significant difference in IL-6 levels between the two groups before and after treatment ($p>0.05$); a represented the IL-6 level compared with the observation group at T3, $p<0.05$; b represented the IL-6 level compared with the observation group at T4, $p<0.05$.

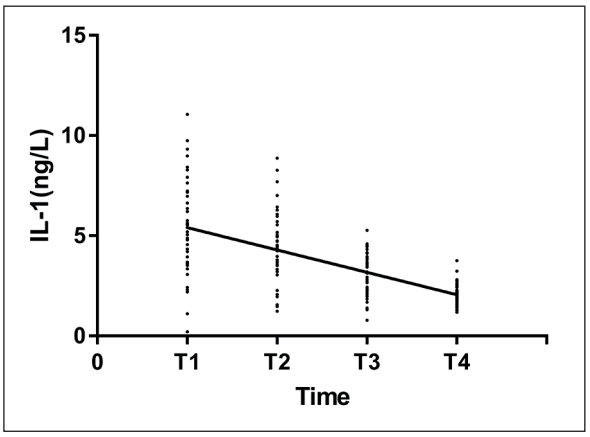

Figure 3. Abscissa 1, 2, 3, and 4 sub-tables represented the correlation analysis of different time periods T1, T2, T3, T4, IL-1 and time of treatment. Spearman correlation analysis showed that IL-1 in the observation group was negatively correlated with the time of treatment, r=-0.657, $p<0.001$.

interleukin-1 (IL-1) has been shown to play an important role in the pathogenesis of inflammation in most autoinflammatory diseases. Therefore, inhibition of IL-1 is a logical step in controlling inflammation in these autoinflammatory diseases[23]. IL-6 is a pleiotropic cytokine that has a broad role in integrating immune responses. One of the roles of IL-6 is to support immune activity, which was defined as the host's ability to respond to infection. IL-6 can act through classical or trans-signaling pathways that have different effects on immune activity[24]. In this study, the therapeutic effect of naloxone combined with acyclovir on children with viral encephalitis was

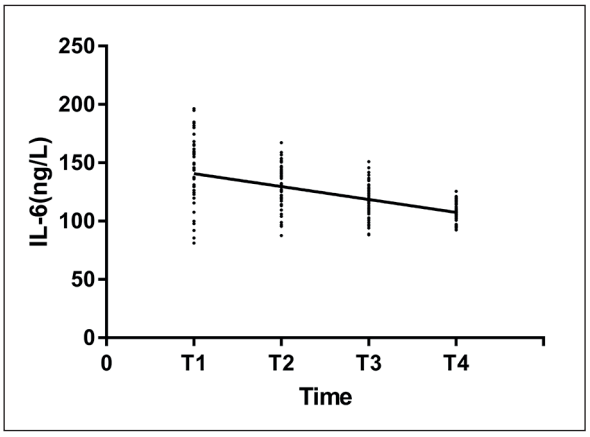

Figure 4. Abscissa 1, 2, 3 and 4 sub-tables represented the correlation analysis of different time periods T1, T2, T3, T4, IL-6 and time of treatment. Spearman correlation analysis showed that IL-6 in the observation group was negatively correlated with the time of treatment, r=-0.545, $p<0.001$.

Table VIII. IL-1, IL-6 and correlation analysis of the time of treatment.

	IL-1	IL-6
r	-0.657	-0.545
95% CI	-0.730 – -0.568	-0.637 – -0.437
p	< 0.001	< 0.001

explored. The combination therapy can effectively make up for the limitations of naloxone in clinical practice, and provide reliable practical basis for the treatment of viral encephalitis in children. It is of great significance for the future clinical treatment of children with viral encephalitis.

In previous studies, patients were treated with acyclovir and the diagnosis was confirmed by one or more of the following: First is the herpes simplex virus culture from brains; second, the herpes simplex virus antibody titer in cerebrospinal fluid increased by 4 times or more; third, herpes simplex virus DNA was detected in cerebrospinal fluid. The results was that 42 patients diagnosed with herpes simplex encephalitis. Five patients (12%) died within the first month. Three patients (7%) had severe neurological sequelae and died after a longer interval. Only one of the 34 surviving patients had neurological symptoms or abnormal neurological examination, or both. Twenty patients (48%) performed daily activities before herpes simplex encephalitis; nine patients (21%) lived independently, but the functional level was lower than that before the disease; five patients (12%) had severe neurological deficits and 29 of 34 survivors were assessed 6 to 11 years after herpes simplex encephalitis. The most common long-term symptoms were dysmnesia (69%), personality and behavioral abnormalities (45%), and epilepsy (24%)[25]. Therefore, we know that although acyclovir reduced the mortality of herpes simplex encephalitis, 30% of patients in this group died or had severe neurological deficits. The other 70% of patients regain independence in their daily activities, but most of these people have persistent neurological symptoms or signs, or both[26]. However, that study only investigated the single use of acyclovir in the treatment of herpes simplex encephalitis. Our study employed acyclovir combined with naloxone in the treatment of viral encephalitis, and analyzed expressions of levels on interleukin IL-1 and IL-6,expressions of levels on different clinical features as well as correlation between the time of treatment of patients in the two groups

before and after treatment. These data greatly increased the scope and accuracy of the study. This study retrospectively analyzed 96 children with viral encephalitis admitted to our hospital. The children were divided into two groups; the control group received acyclovir treatment, and the treatment in the observation group was combined with naloxone on the basis of the control group. The results showed that the clinical efficacy of the observation group was better than that of the control group ($p<0.05$). The prevalence rate of adverse reactions and sequelae, as well as concentration expressions of IL-1 and IL-6 in the observation group were lower than those in the control group during the four periods of treatment ($p<0.05$). Thus, acyclovir combined with naloxone for the treatment of children viral encephalitis had better clinical effects.

However, there are still some defects in this study. Both groups of children have different degrees of adverse reactions during the treatment. Acyclovir neurotoxicity could lead to status epilepticus, hallucinations and changes in consciousness[27]. According to relevant materials, symptomatic bradycardia may occur with acyclovir[28]; common side effects include nausea, diarrhea, headache, dizziness and mental changes[29]. Naloxone is an opioid antagonist used to reverse the effects of opioids. Adverse reactions to this drug include high blood pressure, ventricular arrhythmias, sudden cardiac arrest, epilepsy, and rare pulmonary edema[30]. Epilepsy symptoms in the observation group were most likely caused by adverse reactions of naloxone. Although the incidence rate of these adverse reactions is low, more comprehensive studies are still needed in the next experiment due to the limited conditions of our present study.

Conclusions

In summary, naloxone combined with acyclovir in the treatment of children viral encephalitis have significant effects. It could improve the power of clinical cure, effectively reduce serum indicators such as IL-1 and IL-6 and decrease the occurrence rate of adverse reactions and sequelae, and is expected to be the best choice for the treatment of children viral encephalitis in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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