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Original Article

Efficacy and safety of methylprednisolone sodium succinate combined with gamma globulin in short-term intensive treatment of severe encephalitis in children

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Abstract: Objective: This study aimed to investigate the efficacy and safety of methylprednisolone sodium succinate (MPSS) combined with gamma globulin in the short-term intensive treatment of severe encephalitis in children. Methods: A total of 100 children with severe encephalitis were enrolled and equally divided into Group A (basic treatment + treatment with methylprednisolone (MP)) and Group B (short-term intensive treatment with gamma globulin on the basis of Group A) according to a random number table. Their clinical efficacy, recovery, and adverse reactions after treatment were compared. The Fugl-Meyer assessment (FMA) was used to score the children's motor function. An enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of serum interleukin-6 (IL-6) and tumor necrosis factor (TNF-α). Results: The total effective rate in Group B was significantly higher than the rate in Group A ($P<0.05$). After treatment, the recovery and the FMA score in Group B were better than they were in Group A ($P<0.001$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). After treatment, the levels of serum IL-6 and TNF-α in the two groups significantly decreased ($P<0.05$), and the levels in Group B were significantly lower than those in Group A ($P<0.001$). Conclusion: MP combined with gamma globulin has better efficacy than MP alone in the treatment of children with viral encephalitis and does not increase its toxic and side effects. Additionally, the combination can significantly reduce the levels of serum IL-6 and TNF-α in children.

Keywords: Severe encephalitis, methylprednisolone, gamma globulin, safety

Introduction

Encephalitis is a serious nervous system disease accompanied by cerebral parenchymal inflammation. The United States has more than 20,000 hospitalized cases related to the disease every year, and nearly half of the surviving cases that suffer from permanent nerve injury need long-term care [1, 2]. Encephalitis commonly occurs in pediatrics, and its incidence in children is annually at 4.02 cases/100,000 people in England [3]. There are currently more than 100 viruses that are the most common pathogens known to cause encephalitis, and virus-induced encephalitis is called viral encephalitis [4]. Viral encephalitis is a major cause of acute neurological dysfunction and permanent disability in children all over the world [5]. Although the disease seriously and negatively affects patients and their families, bringing huge economic and medical burdens to them, it cannot be specifically treated at present. Therefore, exploring the therapeutic methods with better efficacy and safety is of great significance for patients with viral encephalitis and their families.

Currently, intravenous corticosteroids or immunoglobulin is effective in the treatment of children or adolescents suffering from viral encephalitis [6]. Methylprednisolone (MP) is a synthetic glucocorticoid with strong anti-inflammatory, immunosuppressive, and anti-allergic activities [7]. Gamma globulin is a therapeutic polyclonal immunoglobulin preparation prepared from mixed human plasma. This preparation is rich

in IgG antibodies and has anti-over immune and immunosuppressive effects, so it has been widely used to treat autoimmune and inflammatory diseases [8, 9]. Viral encephalitis leads to a series of immune responses and activates immune cells to release a large number of cytokines, which enter the central nervous system through the blood-brain barrier (BBB) and then cause brain tissue injury [10]. Short-term intensive treatment refers to the short-term and large-dose administration of drugs to relieve the condition as much as possible. It inhibits the reproduction and spread of viruses and enhances the host's resistance and immunity to viral infection, thus reducing inflammatory infection. Studies have shown that cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) are abnormally expressed in patients with viral encephalitis and involved in the development of the disease [11, 12].

There are currently few studies published on MP combined with gamma globulin in the short-term intensive treatment of viral encephalitis in children, which was therefore explored in this study, so as to explore the efficacy and safety of the combination in treating the disease.

General information and methods

General information

A total of 100 children with viral encephalitis admitted to Xuzhou Children's Hospital Affiliated to Xuzhou Medical University from January 2017 to December 2018 were enrolled, and equally divided into Group A and Group B according to a random number table. The inclusion criteria were as follows: children who met the diagnostic criteria for viral encephalitis [13]; children diagnosed with viral encephalitis through imaging (CT and MRI) and cerebrospinal fluid examinations; children aged 6-12 years old; children with a disease course not longer than 10 days; children whose guardians signed the informed consent form. The exclusion criteria were as follows: children with contraindications to drugs used in this study; children with cardiovascular diseases, immune diseases, or other nervous system diseases. The family members of the children fully understood the process and purpose of this study and signed the informed consent forms. The study was approved by the Ethics Association of Xuzhou Children's Hospital Affiliated to Xuzhou Medical University.

Therapeutic methods

All children were treated basically, which included the maintenance of water and electrolyte balance, nutrition supply, antiplatelet aggregation, oxygen inhalation, and cooling. On the basis of the basic treatment, the children in Group A were intravenously dripped with methylprednisolone sodium succinate (MPSS) that was diluted with an injection of glucose injection or normal saline (Sinopharm Group Rongsheng Pharmaceutical Co., Ltd.) at 10 mg/kg per day. After 3-days of administering this medication, the dosage was reduced to 225 mg/d for 3 days, and then the administration was discontinued. On the basis of the Group A, children in Group B were intravenously injected with gamma globulin (Shanghai RAAS Blood Products Co., Ltd, China) at 1 g/kg per day for 2 days. The children in both groups were treated for 6 consecutive days.

Outcome measures

In this study, the major indicators were clinical efficacy and adverse reactions, and the secondary indicators were motor function scores and recovery.

Efficacy evaluation [14]: Cured indicated that the clinical symptoms completely disappeared, and the imaging and cerebrospinal fluid examinations showed normal. Effective indicated that the symptoms were partially relieved, and the examinations showed partial improvement. Ineffective indicated that the symptoms were not significantly relieved, and the examinations showed deterioration or no improvement. Total effective rate = (cured + effective cases)/total number of cases × 100%.

The Fugl-Meyer assessment (FMA) [15] was used to evaluate the motor function in the two groups, with 50 items and 100 points in total. The highest score of each item was 2 points. A higher score indicated a better motor function.

The recovery and adverse reactions in the two groups after treatment were observed. The recovery consisted of the recovery time from the disturbance of consciousness, the time to the disappearance limb paralysis, the time to the reduction of temperature and fever, and the time to the disappearance of the signs of meningeal irritation. The adverse reactions consist-

Table 1. Comparisons of the general information ([n (%)], x ± sd)

Category	Group A (n=50)	Group B (n=50)	X^2/t	P
Gender			0.657	0.418
Male	23 (46.00)	19 (38.00)		
Female	27 (54.00)	31 (62.00)		
Average Age (years)	8.45±2.56	8.96±2.76	0.958	0.340
Average duration (days)	6.11±2.37	6.77±2.98	1.226	0.223
Average weight (kg)	18.66±3.76	17.87±4.12	1.001	0.319
Place of residence			1.333	0.248
Urban area	15 (30.00)	10 (20.00)		
Rural area	35 (70.00)	40 (80.00)		
Dietary preference			1.714	0.190
Mild test	38 (76.00)	32 (64.00)		
Heavy test	12 (24.00)	18 (36.00)		
Mode of birth			1.980	0.159
Vaginal delivery	24 (48.00)	31 (62.00)		
Cesarean section delivery	26 (52.00)	19 (38.00)		

Table 2. Comparison of clinical efficacy [n (%)]

Group	Markedly effective	Effective	No effect	Total effective rate
Group A (n=50)	12 (24.00)	21 (42.00)	17 (34.00)	33 (66.00)
Group B (n=50)	22 (44.00)	23 (46.00)	5 (10.00)	45 (90.00)
X^2				8.319
P				0.004

ed of gastrointestinal hemorrhage, hepatic injury, renal injury, nausea and vomiting, and skin pruritus.

Measurement of the serum IL-6 and TNF-α concentrations

Fasting venous blood (3 mL) was drawn in the morning before and after treatment and sent to the laboratory for centrifugation. The supernatant, namely serum, was aspirated and then stored in a refrigerator at -70°C to be quantified. All the specimens were measured within 1 month. The serum was removed from the freezer, dissolved in a refrigerator at 4°C, and then completely dissolved at room temperature. The concentrations of serum IL-6 and TNF-α were determined using an enzyme-linked immunosorbent assay (ELISA), with the steps carried out in strict accordance with the instructions of human IL-6 ELISA (Shanghai Qiaoyu Industrial Co., Ltd., China, QN-PS0049) and human TNF-α ELISA (Shanghai Guangrui Biological Technology Co., Ltd., China, R-1389) kits. The optical density (OD) values of each well were determined at 450 nm using a multifunctional microplate reader (Bio-Tek, USA, model: DLK0001622), so as to calculate the concentrations of IL-6 and TNF-α.

Statistical methods

SPSS 18.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. Count data were expressed as the number of cases/percentage [n (%)], and the comparisons of the data between the groups were analyzed using a chi-square test or a corrected chi-square test. The measurement data were expressed as the means ± standard deviations ($\bar{x}$ ± sd), and the comparisons of the data between the groups were analyzed using independent samples t tests, and the comparisons within groups before and after treatment were analyzed using paired t tests. When P<0.05, the difference was considered statistically significant.

Results

Comparison of general information

There were no significant differences between Group A and Group B in terms of gender, average age, average course of the disease, average body weight, place of residence, food preference, or mode of delivery (P>0.05). See **Table 1**.

Comparison of clinical efficacy

Both therapeutic methods were effective in the treatment. After the treatment, the total effective rate in Group B was significantly higher than the total effective rate in Group A (P<0.05). See **Table 2**.

Comparison of the times to symptom alleviation after treatment

After treatment, compared with the children in Group A, the children in Group B had better recovery times from the disturbance of con-

Table 3. Comparison of the time to symptom alleviation after treatment (d, x ± sd)

Groups	Time to recovery from the disturbance of consciousness	Time to the disappearance of limb paralysis	Time to the reduction of temperature and fever	Time to the disappearance of the signs of meningeal irritation
Group A (n=50)	9.71±2.11	8.35±2.14	6.24±1.78	6.34±2.53
Group B (n=50)	6.14±1.56	5.24±2.42	3.56±1.28	4.23±1.89
t	9.620	6.807	8.644	4.724
P	<0.001	<0.001	<0.001	<0.001

Table 4. Comparison of the FMA scores before and after treatment (scores, x ± sd)

Group	Before treatment	After treatment	t	P
Group A (n=50)	24.24±4.24	56.89±7.14	27.802	<0.001
Group B (n=50)	22.89±3.56	72.34±5.42	53.922	<0.001
t	1.724	12.187		
P	0.088	<0.001		

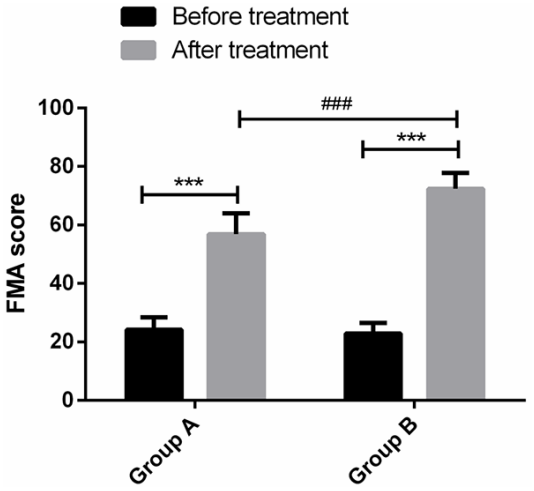

Figure 1. Comparison of the FMA scores before and after treatment. Compared with before treatment within each group, ***P<0.001; Compared with group A, ###P<0.001. Fugl-Meyer assessment, FMA.

sciousness, times to the disappearance of limb paralysis, times to the reduction of temperature and fever, and times to the disappearance of the signs of meningeal irritation (P<0.001). See **Table 3**.

Comparison of the FMA scores before and after treatment

Before treatment, there was no significant difference in the FMA scores between Groups A and B (P>0.05). After treatment, the scores in both groups significantly increased (P<0.001), and the score in Group B was significantly higher than the score in Group A (P<0.001). See **Table 4** and **Figure 1**.

Comparison of the incidence of adverse reactions

After treatment, the children in both groups suffered from adverse reactions, but there was no significant difference in the incidence of the adverse reactions between the two groups (P>0.05). See **Table 5**.

Changes in the serum IL-6 and TNF-α levels before and after treatment

Before treatment, there were no significant differences in the serum IL-6 and TNF-α levels between Groups A and B (P>0.05). After treatment, the levels in both groups significantly decreased (P<0.05), and the levels in Group B were significantly lower than the levels in Group A (P<0.001). See **Table 6** and **Figure 2**.

Discussion

After infecting the patient, the virus destroys the BBB and enters the nervous system, resulting in cerebral inflammation and edema, thereby causing the patient to suffer from fever, changes in consciousness level, headache, focal neurological deficits, and epilepsy [16]. At present, many drugs are commonly used in the clinical treatment of viral encephalitis, including acyclovir, MP, and human serum albumin [17]. Different medication methods have different effects on the treatment, so the efficacy and safety of MP combined with gamma globulin in the short-term intensive treatment of viral encephalitis in children were explored in this study.

A large amount of MP, a glucocorticoid, activates and rapidly increases intracellular steroid receptors. Moreover, this glucocorticoid reduc-

Table 5. Comparison of the incidence of adverse reactions ([n (%)])

Adverse reaction	Group A (n=50)	Group B (n=50)	X^2	P
Gastrointestinal bleeding	3 (6.00)	4 (8.00)	0.000	1.000
Liver function damage	2 (4.00)	1 (2.00)	0.000	1.000
Renal dysfunction	1 (2.00)	2 (4.00)	0.000	1.000
Leukocytopenia	2 (4.00)	3 (6.00)	0.000	1.000
Nausea and vomiting	2 (4.00)	6 (12.00)	1.223	0.269
Itchy skin	5 (10.00)	3 (6.00)	0.136	0.712
Total incidence rate	15 (30.00)	19 (38.00)	0.713	0.398

Table 6. Changes in the serum IL-6 and TNF-α levels before and after treatment (ng/L, x ± sd)

Group	IL-6		TNF-α	
	Before treatment	After treatment	Before treatment	After treatment
Group A	49.12±2.82	31.72±1.94*	56.23±8.72	34.92±5.92*
Group B	48.73±2.43	19.92±2.51*	57.82±7.98	22.78±4.75*
t	0.741	26.302	0.951	11.310
P	0.461	<0.001	0.344	<0.001

Note: Compared with before treatment within each group, *P<0.05.

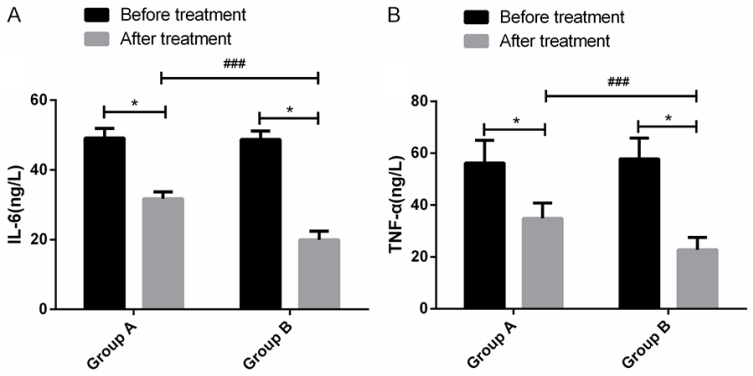

Figure 2. Changes in the serum IL-6 and TNF-α levels before and after treatment Compared with before treatment within each group, *P<0.05; Compared with group A, ###P<0.001.

es the levels of inflammatory cytokines and superoxide free radicals, relieves lipid oxidation, and plays an anti-inflammatory role, thus protecting the BBB [18, 19]. In addition to regulating the activity of macrophages, gamma globulin inhibits the over-activation of the macrophages and the activities of T lymphocytes and natural killer cells, thereby reducing the levels of the autoimmune responses. Moreover, gamma globulin is rich in anti-inflammatory cytokines, so it can neutralize the over-release of inflammatory cytokines after infection and then reduce the inflammatory responses [20, 21]. A study analyzed and compared the efficacy and safety between dexamethasone (DEX), and MP combined with gamma globulin in the treatment of patients with acute myelitis. The results showed that MP combined with gamma globulin was more effective than DEX in the treatment and that it could improve the patients' muscle strength. The study also showed that MP and gamma globulin have a synergistic effect, so they can jointly relieve inflammatory responses, restore neurological function, and reduce immune abnormalities [22]. Another study compared the efficacy and safety between MP alone and MP combined with gamma globulin in the treatment of myasthenia in children. The results showed that MP combined with gamma globulin has a higher total effective rate, a significantly shorter symptom alleviating time, and a significantly shorter total hospitalization time [23]. These studies indicate that MP and gamma globulin have a synergistic effect. The results of this study also show that MP combined with gamma globulin has better efficacy and safety in the treatment of viral encephalitis in children, and that the combination can improve the children's motor functions.

Cytokines are the major regulatory factors of immune responses and the core of inflammatory process. Encephalitis is cerebral parenchymal inflammation caused by infection, post-infection complications, or autoimmune processes [24, 25]. As a pro-inflammatory cytokine and an immunoregulatory cytokine, IL-6 helps the host to defend against infection and

tissue injury, but its abnormal expression in the human body leads to various diseases [26]. TNF-α is a protein mainly produced by activated macrophages and monocytes, involved in human inflammatory and immune responses, and essential to maintain an in vivo balance [27]. Therefore, reducing the level of TNF-α or blocking the binding of TNF-α to its receptors can reduce inflammatory injury [28]. Studies have shown that IL-6 and TNF-α are highly expressed in the cerebrospinal fluid of children with viral encephalitis, and their levels are positively correlated with the severity of the disease. Therefore, the levels of IL-6 and TNF-α are related to the progression and condition of viral encephalitis [29]. IL-6 and TNF-α are highly expressed in the serum of children with viral encephalitis, and their levels after treatment are significantly lower than before treatment [30]. In this study, after treatment, the levels of serum IL-6 and TNF-α in the two groups significantly decreased, and the levels in Group B were significantly lower than the levels in Group A. This suggests that the detection of changes in the levels of serum IL-6 and TNF-α in children with viral encephalitis may provide an effective reference for the progression of and the efficacy for the disease.

Although this study confirmed that MP combined with gamma globulin had better efficacy and safety than MP alone in treating viral encephalitis in children, there are still deficiencies. For example, the levels of serum IL-6 and TNF-α at different time points were not measured. The specific mechanisms of MP and gamma globulin in the treatment were not explored. The optimal dosage of MP combined with gamma globulin in the treatment was not investigated. These deficiencies will be addressed through more experiments in later studies.

In summary, MP combined with gamma globulin has a better efficacy than MP alone in the treatment of children with viral encephalitis and does not increase its toxic and side effects. Additionally, the combination can significantly reduce the levels of serum IL-6 and TNF-α in children.

Disclosure of conflict of interest

None.

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