ORIGINAL ARTICLE

Effectiveness of gamma globulin combined with methylprednisolone sodium succinate in severe hand foot mouth disease — Baoding Children's Hospital, China

Chang Jie, Han Li-po, Zhang Yu, Zhang Yuan-da

Abstract

Objective: To determine the curative effect of gamma globulin combined with methylprednisolone sodium succinate on paediatric patients with severe hand-foot-mouth disease and analyse its influence on cardio-pulmonary functions.

Methodology: Eighty paediatric patients with severe hand-foot-mouth diseases (HFMD) treated in Baoding Children's Hospital, Key Laboratory of Clinical Research on Respiratory Digestive Disease from January 2015 to January 2017 were selected. This study was designed as a case control study with equally dividing patients into test and control groups through random digital method. Patients in the control group accepted methylprednisolone sodium succinate treatment based on conventional therapy. Those in the test group accepted gamma globulin combined with methylprednisolone sodium succinate. The efficacy of the two groups were observed and compared and the improvement of cardiac function index was detected after 3 days of treatment.

Results: The time for symptom remission and hospitalisation of children in the test group were significantly shorter than those in the control group ($P<0.05$). The differences between the two groups had no statistical significance in terms of PaO2, PaCO2, OI, HR, EF% and CO before treatment. After the treatment, patients in the test group had significant improvement compared with the control group ($P<0.05$).

Conclusion: Curative effect of gamma globulin combined with methylprednisolone sodium succinate on paediatric patients showed significance and this treatment could be effectively improve clinical symptoms and cardio-pulmonary functions of paediatric patients.

Keywords: Hand, Foot and Mouth Disease; Gamma Globulin; Methylprednisolone Hemisuccinate (JPMA 70: 1679; 2020)
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Introduction

Hand-foot-mouth disease (HFMD) incidence rate in China has presented year-on-year growing trend in recent years.[1,2] Severe HFMD paediatric patients mainly have symptoms like continuous high fever, nausea and vomiting, poor spirit and convulsion, accompanied by neurogenic pulmonary oedema and cardio-pulmonary failure, which may be related to the fact that EV71 is of neurovirulence. Individuals suffer from rapid progression of illness and if not treated timely, case fatality rate would be high.[3-5] At present, the treatment modalities are not effective for severely ill children.[6] Common clinical HFMD therapeutic methods include anti-virals, control of intracranial pressure and prevention of stress ulcers meanwhile, antibiotics are used for anti-infective therapy with symptomatic and supportive treatments like water replenishing and electrolyte balance are given according to the condition.[7,8] There is no therapeutic measure of specific curative effect for HFMD concurrent with cardio-pulmonary failure; symptomatic and supportive treatment dominates and early-stage intervening measures could prevent the illness from further development. Furthermore, to combat the infection, earlier the intervention, better the effect and hence the results. When central nervous system is involved, it can cause encephaledema, increased intracranial pressure, nucleus of medulla oblongata, nucleus of solitary tract and other dysfunctions, as well as overexcitation of sympathetic nervous system. Moreover, general vasoconstriction, increased circulatory resistance and arterial pressure, reduced Left ventricular ejection fraction (LVEF), reactive high pressure in left ventricle, obstruction of intrapulmonary blood backflow and enhanced capillary permeability can also occur.[9]

Gamma globulin contains opsonic and neutralising antibodies for susceptible microorganisms of normal people. It can directly centralise toxins, assist in killing pathogens, regulate immunological cell functions, inhibit activation of lymphocytes and cytophagocytosis of mononuclear-phagocytes, seal Fc antibodies, reduce generation and excitation of auto-antibodies and alexin, interdict neural cellular immune injury, protect brain cells and promote recovery of brain functions. Furthermore, it can interdict virus replication at an early stage so as to strengthen immunity of the organism.[10,11]

Department of Paediatrics, Baoding Children's Hospital, Key Laboratory of Clinical Research on Respiratory Digestive Disease, Hebei Baoding, China.
Correspondence: Zhang Yuan-da. Email: dii876@163.com

Methylprednisolone sodium succinate is an artificially synthesised glucocorticoid. It can exert its biological effect without conversion through the liver. Methylprednisolone sodium succinate can exert effect through the mechanisms such as direct neurophysiological action, non-specific immunosuppression, inhibition of lipid peroxidation, inhibition of endogenous pyrogen release and improvement of organism stress. Methylprednisolone sodium succinate acts on central nervous system of severe HFMD child patients to generate strong non-specific immunosuppressive action and reduce damage caused by immunocompetent cells in serum and hazardous factors to central nerves.[12] In addition, it can relieve inflammation and edema caused by pathological tissues of acute medullary sheath due to virus infection, reduce demyelination degree and improve peripheral neurological functions.[13] It has been reported in recent years that early-stage full-dose hormone combined with gamma globulin has significant effect on treating hand-foot-mouth disease.[6] This study adopted gamma globulin combined with injection of methylprednisolone sodium succinate for paediatric patients with severe HFMD. The objective of this study was to determine curative effect of gamma globulin combined with methylprednisolone sodium succinate on paediatric patients with severe hand-foot-mouth disease and analyse its influence on cardio-pulmonary functions.

Patients and Methods

This study was retrospective case control, with same sample size of the two groups. Pass software was used to estimate the sample size, that is, each group needed a sample size of 39. The actual sample size of this study was 42 cases, which could meet the requirements. The study was approved by the Institutional Ethics Committee of Baoding Children's Hospital and written informed consent was obtained from all participants.

Eighty-four paediatric patients with severe hand-foot-mouth diseases (HFMD) received and cured from January in 2015 to January in 2017 in Baoding Children's Hospital, Key Laboratory of Clinical Research on Respiratory Digestive Disease were selected and equally divided into 2 groups through random digital method, namely test group and control group. All of the patients were at HFMD stage II without obvious cardio-pulmonary failure signs; they had fever and neurological involvement to different degrees like poor spirit, drowsiness and easily frightened, headache, nausea, vomiting, etc. There were 61 males and 23 females with their ages ranging from 6 months to 5 years old and average age was (14.9±5.8) months.

The inclusion criteria was all patients conformed to diagnostic criteria for severe HFMD;[14,15] all family members understood the test contents and voluntarily participated and signed the informed consent form. The exclusion criteria was paediatric patients with congenital diseases; patients concurrent with multiple organ failures; patients with other severe organ diseases; patients with poor compliance or those quitting in the middle.

After admission, the patient's condition was closely monitored, water electrolyte and acid-base balance were maintained, antipyretic and intravenous vitamin supplementation were given for symptomatic support treatment and ribavirin 10-15mg/(kg/d) was given for antiviral treatment. Based on this treatment, methylprednisolone sodium succinate 10-20mg/(kg/d) was injected for paediatric patients in the control group (Belgium Pfizer Pharmaceuticals Co., Ltd) for continuous 3 days. After 3 days of continuous administration, the drug was cut in half, then treated for 2 days, then cut in half and stopped after 2 days of continuous treatment. Paediatric patients in the test group accepted intravenous injection of immune globulin 1-2mg/(kg/d) (Hualan Biological Engineering, Chongqing branch) for continuous 3 days in addition to the steroids in same dose as controls. Mechanical ventilation was implemented according to their conditions.

Paediatric patients were observed for continuous 1 week. Fever abatement time, deflorescence time, neurological involvement symptoms, white blood cell recovery time and average length of stay of patients in the two groups were observed and compared. After 3 days of combined medication, arterial blood was drawn, accompanied with arterial blood gas analysis. Improvement conditions of pulmonary indexes like PaO2, PaCO2 and oxygenation index (OI) as well as cardiac indexes like heart rate (HR), LVEF% and cardiac output (CO) were compared, ultrasonic cardiogram examination was implemented, LVEF% and CO were calculated.

SPSS22.0 software package was used for data analysis, measurement data were expressed by mean±standard deviation; t-test was used for intergroup comparison while paired t-test was used for intragroup comparison confirming that the data was normally distributed before t-test. Chi-square test or Fisher exact test probability method was used for comparison of enumeration data such as effective comparison, and $p<0.05$ was taken as significance level.

Results

Fourty patients in each group completed the study. Twenty-seven cases in the control group and 22 in the

Table-1: Comparison of the general data of 2 groups of children.

Variables	Test group (n=40)	Control group (n=40)	t or X^2	P
Sex: male/female (%)	29/11 (72.5/27.5)	30/10 (75/25)	0.37	P>0.05
Age (months)	14.91±5.83	15.12±5.61	1.67	P>0.05
Course of disease (h)	92.42±13.61	95.71±14.12	157	P>0.05
Use of ventilator n (%)	27 (67.5)	22 (55)	1.54	P>0.05
Herpes n (%)	30 (75)	28 (70)	0.54	P>0.05
Temperature (°C) ≥39.0/<39.0 (%)	37/3 (92.5/7.5)	39/1 (97.5/2.5)	0.54	P>0.05

Table-2: Clinical symptom subsiding and hospitalization time of 2 groups of children ($\chi \pm SD$).

Variables	Test group (n=40)	Control group (n=40)	T	P
Fever subsided (days)	3.68±1.20	4.85±1.34	6.04	P<0.05
Herpes faded (days)	5.28±0.86	5.70±0.91	3.20	P<0.05
Symptoms of nervous system subsided (days)	3.81±1.05	4.72±1.18	5.37	P<0.05
White blood cells returned to normal (days)	7.43±1.32	4.56±0.82	14.54	P<0.05
Average length of stay (days)	9.46±1.86	13.32±2.30	12.15	P<0.05

Table-3: Comparison of heart and pulmonary function improvement in 2 groups of children ($\chi \pm SD$).

Group	PaO_2 (mmHg)				$PaCO_2$ (mmHg)				OI (mmHg)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Test group	71.4±10.5	97.2±12.4	14.86	<0.01	42.3±6.6	36.3±5.8	10.52	<0.01	147.3±36.4	463.4±57.2	43.71	<0.01
Control group	72.1±10.6	89.5±11.8	10.15	<0.01	45.9±6.4	39.2±6.1	6.86	<0.01	138.5±38.0	389.4±46.5	38.88	<0.01
t	0.37	4.28			0.41	3.13			1.56	9.39		
p value	>0.05	<0.01			P>0.05	<0.01			P>0.05	<0.01		

	HR (time/min)				EF (%)				CO (L/min)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
	183.4±27.6	132.5±23.4	13.10	<0.01	43.5±10.4	62.1±13.6	9.99	<0.01	2.78±0.84	3.57±1.13	5.29	>0.01
	187.4±30.6	164.3±16.5	5.35	<0.01	42.5±10.5	54..1±12.4	6.75	<0.01	2.81±0.88	3.17±0.89	2.48	<0.05
	0.93	7.86			0.69	3.99			0.23	2.56		
	>0.05	<0.01			>0.05	<0.01			P>0.05	<0.05		

*PaO2: partial pressure of artery. PaCO2: partial pressure of carbon dioxide in artery.
OI: Oxygenation index. HR: heart rates. LVEF%: Left ventricular ejection fraction. CO: Cardiac output.

test group accepted mechanical ventilation. Patients in the two groups were of comparability with respect to age, gender, symptoms, treatment and prognosis of disease, with no statistically significant difference (P>0.05) as shown in Table-1.

The time for symptom remission and hospitalisation of children in the test group were significantly shorter than those in the control group (p<0.05) as shown in Table-2.

After treatment for 3 days, there were significant improvements in PaO2, PaCO2, OI, HR, ejection fraction (EF) and CO in the 2 groups (P < 0.05). The PaO2, PaCO2, OI, HR, EF and CO in the experimental group were significantly higher than those in the control group P<0.05) as shown in Table-3.

Discussion

Hand-foot-mouth disease (HFMD), a common infectious disease among children, is mainly caused by neurotropic enterovirus 71 type (EV71) and coxsackie virus A16 type (CoxA16).[16]

At present, there is no specific antiviral therapy for HFMD. Immune globulin is believed to be able to treat severe enteroviruses (EV) infection by reducing the inflammatory

response of the central nervous system (CNS).[17] Studies have shown that in the outbreak of EV-A71 in patients with severe HFMD, high-dose immune globulin treatment has achieved good results. In the absence of fatal cases, part of the reason for improving the prognosis may be the use of immune globulin, especially EV-A71 HFMD cases.[18,19] More children with EV-A71 infection are recommended for immune globulin because of neurological symptoms. However, no prospective randomised trial has been designed to study the efficacy and benefit of immune globulin in the treatment of HFMD. Considering that immune globulin might not contain enough antibodies to neutralise a large number of EV serotypes and subtypes, the systematic application of immune globulin is still controversial. Current research showed that immune globulin could shorten the course of HFMD if given early.

Methylprednisolone sodium succinate, as one of the glucocorticoids, has the effect of inhibiting the release and development of inflammatory factors in human body. Therefore, it could play the following roles in the early treatment of children with the above diseases: effectively inhibiting the inflammatory reaction in children's body; reducing the permeability of children's capillaries, so as to reduce pulmonary and cranial oedema meningeal encephalitis and other complications. These drugs work fast, can effectively control the development of children's condition for a long time, so as to improve their prognosis.[20]

Combined application of immune globulin and methylprednisolone sodium succinate has a favourable collaborative effect, which can not only strengthen anti-inflammatory effect but also can reduce complications caused by hormones like infection diffusion and secondary infection. In this study, HFMD child patients in the test group accepted gamma globulin combined with methylprednisolone sodium succinate treatment based on conventional treatment, while gamma globulin was not used for patients in the control group. Total effective rate in the test group was obviously higher than that in the control group. The time for symptom remission and hospitalisation time of the children in the test group were significantly shorter than those in the control group. This indicated that combined application of gamma globulin and methylprednisolone sodium succinate for treating severe HFMD has significant curative effect. This combined treatment can improve effective rate of severe HFMD treatment, reduce death rate and disability rate of child patients, control their illness within a short time, relieve their cardio-pulmonary functions, effectively prevent HFMD child patients from developing towards cardiopulmonary failure and shorten their length of stay. It has obvious advantages compared with other treatment methods.

Limitation

This study has some shortcomings. First, this study was a retrospective case-control study, which was approved by the hospital's ethics committee and obtained patient consent, but did not receive the RCT number and secondly, the sample size was small.

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