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Original Article

Effect of gamma globulin combined with creatine phosphate on viral myocarditis

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Abstract: Objective: This study aimed to investigate the effect of gamma globulin (IVIG) and creatine phosphate (CP) on viral myocarditis (VMC). Methods: We enrolled 121 young patients with VMC who were admitted in our hospital from February 2017 to September 2018, and divided them into two groups as follows: study group (62 patients, IVIG + CP + routine treatment), and control group (59 patients, conventional treatment). Patient's baseline data, including gender, age, disease course, etiology, cardiac function classification, and severity, were collected. Ejection fraction (EF), fractional shortening (FS), and mitral ratio of peak early to late diastolic filling velocity (E/A ratio) before and after treatment were recorded. These changes include the lactate dehydrogenase, creatine kinase (CK), aspartate aminotransferase, creatine kinase isoenzyme (CK-MB), and cardiac troponin I (CTnI). Furthermore, the changes in immune factors such as $CD3^+$, $CD4^+$, and $CD8^+$ before and after the treatment were determined. Results: The study group had a significantly higher response rate than the control group ($P < 0.05$). After treatment, the ejection fraction, fractional shortening, and mitral ratio of peak early-to-late diastolic filling velocity were more significantly improved in the study group than in the control group ($P < 0.05$). The electrocardiogram (ECG) results of the study group were also significantly better than those of the control group ($P < 0.05$). The levels of lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), creatine kinase isoenzyme (CK-MB), and cardiac troponin I (CTnI) in the study group were all significantly better than those in the control group ($P < 0.05$). Symptom recuperation, cardiac function recovery, and ECG and myocardial enzyme normalization were significantly faster in the study group than those in the control group ($P < 0.05$). The immune factor levels in the study group also significantly improved compared with those before the treatment ($P < 0.05$). Meanwhile, the adverse reactions in both groups showed no differences ($P < 0.05$). Conclusion: IVIG combined with CP exhibited better clinical effects and effectively boosted the immune system of patients with VMC.

Keywords: Viral myocarditis, gamma globulin, creatine phosphate

Introduction

Viral myocarditis (VMC) is an infectious cardiomyopathy that exhibits myocardial limitation and diffuse acute or chronic inflammatory lesions caused by viruses. These viruses not only invade and directly damage the myocardium but also mediate a secondary immune response. VMC commonly affects young individuals. It is characterized by nonspecific manifestations with a high recurrence risk. It is often diagnosed at a later disease stage, causing acquired heart failure, cardiomyopathy, and heart transplantation in children. The mortality rate of adolescent VMC is as high as 21% [1-5].

The routine treatment of VMC includes diuretics, acid-base correction, antibiotics, and antiviral drugs, without specific therapies [6]. Generally, VMC can be cured. However, considering the high mortality rate, it has seriously affected the health of children and adolescents. Combination of drugs with better treatment efficacy needs to be explored to improve the prognosis. Creatine phosphate (CP) serves as a rapidly mobilizable reserve of high-energy phosphates. In patients with VMC, it can be utilized as a myocardial protective agent to restore spontaneous sinus rhythm and reduce myocardial enzyme release [7-9]. In addition, gamma globulin (IVIG) is an immunoregulatory factor that appears to be a promising therapeutic drug for treating myocarditis [10, 11].

In this study, CP and IVIG were combined to treat VMC, and the patient's recovery and

Table 1. Baseline data

	Study group (n = 62)	Control group (n = 59)	χ^2/t	P
Gender [n (%)]			0.896	0.017
male	35 (56.45)	34 (57.63)		
Female	27 (43.55)	25 (42.37)		
Age	7.58 ± 2.16	7.64 ± 2.23	0.147	0.883
Course of disease (days)	13.64 ± 3.61	13.55 ± 3.48	0.140	0.889
Causes			0.683	0.711
Respiratory tract infection [n (%)]	48 (77.42)	46 (77.97)		
Enteritis	10 (16.13)	11 (18.64)		
Other illnesses	4 (6.45)	2 (3.39)		
Cardiac function classification [n (%)]			0.678	0.712
NYHA I	28 (45.16)	30 (20.85)		
NYHA II	25 (40.32)	23 (38.98)		
NYHA III	9 (14.52)	6 (10.17)		
Severity of disease [n (%)]			0.238	0.888
Light	22 (35.48)	20 (33.90)		
Medium	29 (46.77)	30 (50.85)		
Severe	11 (17.74)	9 (15.25)		
White blood cell count	13.25 ± 1.68	13.29 ± 1.57	0.135	0.893

changes in immune function were assessed to explore the effects of this drug combination for clinical reference.

Materials and methods

Enrollment of subjects

This study enrolled 121 patients with VMC who were 1-15 years old and were admitted in our hospital. A total of 62 patients received IVIG + CP + routine treatment, comprising the study group, and 59 patients received routine treatment, comprising the control group. The inclusion criteria were patients who met the diagnostic criteria for VMC [12], who were in the acute phase of disease and did not receive any medication for treatment prior to admission, and those who did not take immune preparations during the past month. Conversely, the exclusion criteria were patients with combined immunodeficiency, congenital heart disease, rheumatic heart disease, bacterial infection, liver and kidney dysfunction, mental illness, or any debilitating disease that could hamper one's participation. An informed consent was obtained from each patient's family or guardian, and the medical ethics committee of Zhangzhou Zhengxing Hospital approved this study.

Treatment methods

All patients were provided with bed rest, oxygen inhalation, vasodilation, diuresis, acid-based correction, antibiotics, and antiviral drugs. At the same time, vitamin C (200 mg/time, 3 times/d, Jamieson Canada), prednisone (1-2 mg/kg.d, taken orally, Jamieson Canada), vitamin B (5-10 mg/time, 2-3 times/d, take after meal, Jamieson Canada), and vitamin E (30 mg/time, 2-3 times/d, taken before meals, Jamieson Canada) were administered to nourish the heart muscle.

In addition to the abovementioned treatment method, the study group was treated intravenously with IVIG (S19994004, Shanxi Kangbao Biological Products Co., Ltd.; 400 mg/[kg·day]) for 3-5 days and CP (H20084021, Hebei Tiancheng Medicin Industry Co., Ltd.; 0.5-10 g/time) once a day for 14 days. The two groups shared the same course of treatment.

Outcome measurements

Patient's baseline data, including gender, age, disease course, etiology, cardiac function classification, and severity, were collected. Two weeks after the treatment, we evaluated the clinical efficacy of the drug combination in both groups and described the efficacy through the

Table 2. Response rate [n (%)]

	Study group (n = 62)	Control group (n = 59)	χ^2	P
Markedly effective	34 (54.84)	27 (45.76)	0.996	0.318
Effective	23 (37.10)	28 (47.46)	1.331	0.249
Ineffective	5 (8.06)	14 (23.73)	5.217	0.022
Response rate	57 (91.94)	45 (76.27)	5.217	0.022

Table 3. Cardiac function

	Study group (n = 62)	Control group (n = 59)	t	P
EF				
Before treatment	51.24 ± 8.76	51.55 ± 8.72	0.185	0.846
After treatment	58.65 ± 8.93*	66.36 ± 8.74*	4.797	< 0.001
FS				
Before treatment	22.35 ± 6.23	22.44 ± 6.17	0.080	0.937
After treatment	35.09 ± 6.95*	26.39 ± 6.41*	7.148	< 0.001
E/A ratio (%)				
Before treatment	0.79 ± 0.13	0.80 ± 0.11	0.456	0.650
After treatment	0.50 ± 0.05*	0.61 ± 0.07*	9.984	< 0.001

Note: *compared within the same group P < 0.05.

Table 4. ECG improvement [n (%)]

	Study group (n = 62)	Control group (n = 59)	χ^2	P
Markedly effective	33 (53.23)	24 (48.98)	0.198	0.657
Effective	25 (40.32)	22 (37.29)	0.117	0.732
Ineffective	3 (6.45)	13 (24.59)	7.603	0.006
Response rate	58 (93.55)	46 (75.41)	7.603	0.006

following terminologies. Markedly effective: Myocardial enzymes and cardiac function normalized, and the symptoms disappeared. Effective: Myocardial enzymes and cardiac function improved compared with those before the treatment but did not normalize; the symptoms also improved. Ineffective: Myocardial enzymes and cardiac function did not improve; symptoms also did not improve, and some even worsened.

Cardiac function measurements

Cardiac function was considered to show improvement according to various echocardiographic changes, such as improved ejection fraction (EF), fractional shortening (FS), and mitral ratio of peak early to late diastolic filling velocity (E/A ratio) before and after treatment.

For instance, the treatment is regarded to be "markedly effective" if the ST segments are normal and the atrioventricular and intra-atrial conduction block have significantly improved. It is "effective" if the ST segment elevation is greater than 0.05 mV but not in normal levels and the atrioventricular and intra-atrial block have improved. In contrast, it is "ineffective" if the ST segment is not elevated and the atrioventricular and intra-atrial block have not improved.

The changes in troponin and myocardial enzymes, as well as adverse reactions records

The changes in troponin and myocardial enzymes, as well as adverse reactions, were recorded. These changes include the lactate dehydrogenase, creatine kinase (CK), aspartate aminotransferase, creatine kinase isoenzyme (CK-MB), and cardiac troponin I (CTnI). Toshiba's automatic biochemical analyzer was used to determine the serum of all patients by the enzyme rate method. Furthermore, the changes in immune factors such as $CD3^+$, $CD4^+$, and $CD8^+$ before and after the treatment were determined. $CD3^+$, $CD4^+$, and $CD8^+$ were automatically detected using a flow cytometer.

Statistical analysis

Data were analyzed by the SPSS 19.0 (Asia Analytics Formerly SPSS China). The measurement data were expressed as [n (%)], and the comparison between the two groups was examined by χ^2 test. Count data were expressed as mean ± standard deviation (mean ± SD), and the comparison between the two groups was analyzed by independent sample *t* test. For the comparison at different time points, we used the analysis of variance with post hoc LSD test. In addition, $P < 0.05$ indicates statistical significance.

Results

Baseline data

The baseline data such as gender, age, disease course, etiology, cardiac function classification,

Table 5. Changes in troponin and myocardial enzymes

	Study group (n = 62)	Control group (n = 59)	t	P
CTnI (μg/L)				
Before treatment	0.31 ± 0.10	0.32 ± 0.09	0.577	0.565
After treatment	0.13 ± 0.05*	0.21 ± 0.07*	7.261	< 0.001
CK (U/L)				
Before treatment	622.33 ± 48.63	630.21 ± 47.54	0.901	0.370
After treatment	276.45 ± 28.69*	189.31 ± 27.51*	17.038	< 0.001
CK-MB (U/L)				
Before treatment	52.06 ± 10.89	52.15 ± 10.51	0.046	0.963
After treatment	23.15 ± 7.35*	34.84 ± 7.69*	8.550	< 0.001
LDH (U/L)				
Before treatment	148.36 ± 21.81	150.33 ± 20.74	0.509	0.612
After treatment	58.36 ± 10.25*	76.34 ± 13.22*	8.384	< 0.001
AST (U/L)				
Before treatment	35.23 ± 2.89	35.49 ± 2.57	0.522	0.603
After treatment	30.15 ± 1.84*	25.31 ± 1.57*	15.529	< 0.001

Note: *compared within the same group P < 0.05.

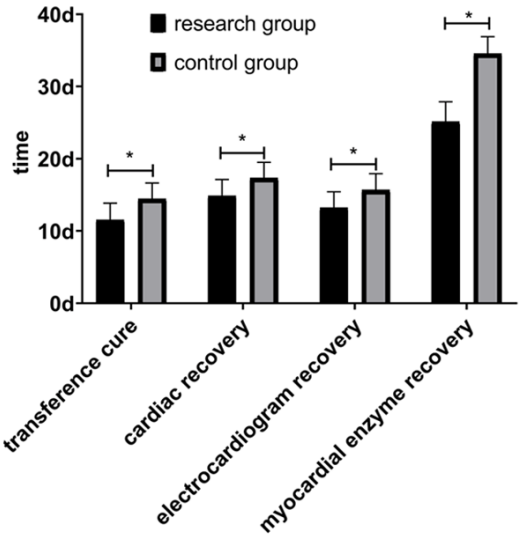

Figure 1. Recovery time. The time duration for the disappearance of symptoms, recovery of cardiac function, recovery of electrocardiogram signals, and recovery of myocardial enzymes was significantly shorter in the study group than in the control group. * Indicates P < 0.05.

severity, and white blood cell count were not significantly different between groups (P < 0.05, **Table 1**).

Response rate comparison

The study group showed a higher response rate than the control group (P < 0.05, **Table 2**).

Cardiac function comparison

Before treatment, the EF, FS, and E/A ratio between the two groups were not significantly different (P < 0.05). After treatment, the study group showed a better cardiac function than the control group (P < 0.05), but a significantly better cardiac function was observed in both groups than that before treatment (P < 0.05, **Table 3**).

Electrocardiogram (ECG) signal comparison

The study group exhibited significantly better ECG signals than the control group (P < 0.05, **Table 4**).

Troponin and myocardial enzyme comparison

Before treatment, the levels of these two indicators had no significant difference between such groups (P < 0.05). After treatment, the study group had significantly better levels than the control group (P < 0.05), but both groups exhibited significant improvement compared with those before the treatment (P < 0.05, **Table 5**).

Recovery time

The time duration for the normalization of symptoms, cardiac function, ECG, and myocardial enzymes was (11.54 ± 2.31), (14.87 ± 2.26),

Table 6. Immune factor levels comparison

	Study group (n = 62)	Control group (n = 59)	t	P
$CD3^+$				
Before treatment	45.54 ± 5.14	44.28 ± 5.31	1.326	0.187
After treatment	58.34 ± 6.37*	50.34 ± 5.67*	7.284	< 0.001
$CD4^+$				
Before treatment	34.15 ± 5.61	34.24 ± 5.47	0.089	0.929
After treatment	41.23 ± 6.02*	35.35 ± 5.87	5.436	< 0.001
$CD8^+$				
Before treatment	22.31 ± 6.04	22.35 ± 6.11	0.036	0.971
After treatment	29.34 ± 6.57*	23.14 ± 6.17	5.357	< 0.001

Note: *compared within the same group P < 0.05.

Table 7. Recovery time

	Study group (n = 62)	Control group (n = 59)	X^2	P
Nausea and vomiting	3 (4.84)	3 (5.08)		
diarrhea	2 (3.23)	2 (3.39)		
irritability	2 (3.23)	1 (1.69)		
leukopenia	5 (8.06)	3 (5.08)		
Total adverse reaction	12 (19.35)	9 (15.25)	0.354	0.552

(13.21 ± 2.21), and (25.15 ± 2.74) days, respectively. In the control group, the time was (14.46 ± 2.17), (17.34 ± 2.16), (15.68 ± 2.25), and (34.57 ± 2.33) days, respectively; with an overall shorter recovery time observed in the study group (P < 0.05, **Figure 1**).

Immune factor level comparison

Both groups exhibited no differences in immune factor levels before treatment (P > 0.05). Meanwhile, after treatment, the study group had significantly better immune factor levels than the control group (P < 0.05) and demonstrated a significant improvement compared with that before treatment. However, $CD3^+$ was the only elevated index in the control group after treatment (P < 0.05, **Table 6**).

Adverse reaction comparison

The adverse reactions between the two groups were not significantly different (P < 0.05), and no serious adverse reactions were observed in both groups (**Table 7**).

Discussion

VMC is characterized by myocardial inflammation, causing acute myocarditis, dilated cardiomyopathy, and congestive heart failure. It is one of the common causes of sudden death in young adults. Furthermore, VMC is caused by excessive inflammation and autoimmune responses resulting from viral infections. However, the mechanism of VMC remains unclear. Although VMC can be self-healed, it can still be detrimental. Hence, new diagnostic technologies and targeted therapies are being developed. Unfortunately, specific therapies for VMC remain unestablished. Therefore, exploring a more effective drug treatment for VMC is necessary [13-15].

No significant differences in baseline data were found between both groups. The study group showed better response rate and cardiac function (i.e., EF, FS, and E/A ratio) than the control group. After treatment, the study group also exhibited significantly better ECG signals and troponin and myocardial enzyme levels than the control group.

Meanwhile, the normalization of symptoms, cardiac function, ECG signals, and myocardial enzymes in the study group was significantly faster than that in the control group. Furthermore, the study group had significantly better $CD3^+$, $CD4^+$, and $CD8^+$ levels than the control group after treatment, but no differences in the adverse reaction rate were found between both groups.

Xin Ji Kang capsules combined with CP showed significant clinical effects in children with VMC [16]. In addition, CP combined with captopril or CP combined with adenosine triphosphate disodium can effectively improve the clinical effects, increase myocardial enzyme activity, and reduce the chance of occurrence [8, 17]. Thus, CP is clinically effective and safe. The pathogenesis of VMC includes both direct damage mediated by viral infections and indirect damage caused by the host immune response. Myocarditis can develop into dilated cardiomyopathy, which is related to immune pathogenesis. T cell-mediated or/and antibody-mediated autoimmunity, as well as innate immunity, work

together to cause myocarditis and dilated cardiomyopathy [18-20].

IVIG participated in the cellular responses and humoral immune responses, exhibiting dual immunosuppressive effects. It can inhibit virus replication by employing specific neutralizing antibodies and suppress antibody production by clearing the monocytes and macrophages, thereby reducing the myocardial inflammation responses. In addition, IVIG can regulate T cell subsets, down-regulate cellular immunity, and reduce the cytotoxic activity. After the inflammation has been eliminated, eradication of Parvovirus B19 and Human Herpes Virus 6 still pose a challenge [21, 22]. In our study, the $CD3^+$, $CD4^+$, and $CD8^+$ levels in the study group were significantly better than those before the treatment, but the $CD3^+$ level only elevated in the control group; thus, IVIG can effectively strengthen the immune system. In previous studies, treatment of complete heart block, cardiogenic shock, and pulmonary edema via intravenous IVIG infusion therapy effectively improved cardiopulmonary function within 6 hours [23, 24].

However, our study has some limitations. The sample size is not sufficiently large; hence, the experimental results need further confirmation. In addition, the drugs we explored may not be the best combination. We hope to improve the regimen in future experiments.

In conclusion, IVIG combined with CP exhibited satisfactory efficacy and effectively improved the immune levels of patients with VMC.

Disclosure of conflict of interest

None.

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