Am J Transl Res 2022;14(12):8659-8667
www.ajtr.org /ISSN:1943-8141/AJTR0147345

Original Article

Therapeutic effect of captopril combined with phosphocreatine sodium on viral myocarditis

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Received October 29, 2021; Accepted November 21, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Objective: To analyze the therapeutic effect of captopril combined with phosphocreatine sodium in patients with viral myocarditis. Methods: A total of 140 patients with infectious myocarditis who received treatment in Hanzhong City People's Hospital from December 2019 to January 2022 were retrospectively enrolled as study subjects. 61 of them were treated with captopril and constituted the control group (CG), and the remaining 79 who received phosphocreatine sodium in addition to captopril were the research group (RG). Variables were observed and compared between the two groups, including clinical efficacy, adverse reactions during treatment, and changes in myocardial enzymes, cardiac function, troponin, and inflammatory factors. According to therapeutic effect, those patients with marked results were categorized as the significant improvement group, and those whose results were just effective or ineffective were the insignificant improvement group. The risk factors affecting the efficacy of the patients were analyzed by logistic regression. Results: Compared to the CG, the RG had greater decreases in aspartate aminotransferase (AST), creatine kinase isoenzyme (CK-MB), creatine kinase (CK), and lactate dehydrogenase (LDH) (all $P < 0.05$). The left ventricular ejection fraction (LVEF), left ventricular fractional shortening (FS), and left ventricular stroke volume (SV) in the RG increased significantly more after treatment ($P < 0.05$), while the levels of high-sensitivity troponin I (cTnI) and cardiac troponin T (cTnT) decreased more significantly ($P < 0.05$) compared to the CG. The levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in the RG were more down-regulated ($P < 0.05$), and they had a higher overall response rate after treatment ($P < 0.05$). However, there was no significant difference in the incidence of adverse reactions between these two groups ($P > 0.05$). Multivariate logistic regression analysis showed that CK-MB, LVEF, cTnI, and cTnT were independent factors affecting the efficacy. Conclusion: Captopril combined with phosphocreatine sodium can reduce the inflammatory response in patients with infectious myocarditis, improve cardiac function, and improve the therapeutic efficacy.

Keywords: Captopril, phosphocreatine sodium, viral myocarditis

Introduction

Myocarditis refers to inflammatory diseases characterized by necrosis of cardiomyocytes and infiltration of interstitial inflammatory cells caused by various causes and divided into two categories: infectious and non-infectious [1]. Infectious causes principally include viruses, spirochetes, rickettsiae, protozoa, helminths, and molds; non-infectious causes are allergic myocarditis and myocarditis caused by physicochemical factors or drug toxicant factors [2]. Viral myocarditis is the most common infectious factor, and it is commonly distributed at all ages worldwide, although myocarditis caused by rheumatic fever and diphtheria has gradually decreased, especially among children and adults under 40 [3]. Nowadays, more than 20 viruses causing myocarditis have been identified, of which the more common ones are viruses infected in the upper respiratory tract and intestine, mainly including coxsackievirus B, adenovirus and echovirus, influenza virus, hepatitis, and parainfluenza [4]. Due to the deficiency of specificity in test results, it is difficult to confirm the diagnosis that mainly based on a comprehensive judgment of the patient's prodromal infection symptoms, cardiac-related manifestations, myocardial injury, abnormal ECG, etiology, and other examination results.

Lack of uniform criteria can easily lead to misdiagnosis [5, 6], missed optimal timing for treatment, and a greater burden on patients, families and society.

There is no completely effective treatment for myocarditis currently, and the existing ones mainly focus on adequate rest of patients, supportive treatment, and early management of complications. Captopril is a common angiotensin-converting enzyme inhibitor that reduces angiotensin production by inhibiting local vascular and circulatory systems of body tissues, mostly used in the treatment of hypertension, diabetes, and coronary heart disease [7, 8]. Early studies have revealed that captopril can improve the condition of patients with severe myocarditis, as well as alleviating heart failure [9]. Creatine phosphate is an endogenous high-energy compound that is widely present in myocardial tissue [10], and also an exogenous myocardial cell protectant that is safe, reliable, and effective. It penetrates the cell membrane and maintains a stable level of high energy phosphate in myocardial cells, while it acts on oxygen free radicals and avoids the peroxidation damage of myocardial cells from free radicals by reducing oxygen free radicals, thus playing a role in protecting myocardial cells [11]. Previously, Niu et al. [12] found that phosphocreatine sodium achieved 100% efficacy in the treatment of 124 children with viral myocarditis. However, whether captopril combined with phosphocreatine sodium has a better effect in the treatment of adults has not yet been reported.

In this study, we retrospectively analyzed the therapeutic effect of captopril combined with phosphocreatine sodium in patients with viral myocarditis and analyzed the influencing factors affecting treatment efficacy to provide a reference for selection of clinical treatment.

Materials and methods

Clinical data

A total of 140 patients with infectious myocarditis who received treatment in Hanzhong City People's Hospital from December 2019 to January 2022 were retrospectively enrolled as the study subjects. 61 of them treated with captopril were grouped as a control group (CG), and the remaining 79 who got phosphocreatine sodium in addition to captopril were the research group (RG). This study was approved and conducted by the medical ethics committee of Hanzhong City People's Hospital (Ethical batch No.: 2019 (L) 091).

Inclusion and exclusion criteria

Inclusion criteria: Patients in line with the diagnostic criteria for viral myocarditis [13]; patients with cardiac function evaluated as grade II-III; patients with no other antiviral drugs used in the past 1 month; patients with no severe liver, kidney and lung or other solid organ diseases; patients with complete clinical data; and patients aged > 18 years.

Exclusion criteria: Pregnant and lactating patients; patients with allergy to the study drug; patients combined with malignant tumor; patients with primary immunodeficiency disease; patients combined with other serious diseases; or patients with mental illness.

Treatment regimen

Patients in both groups received treatments including rest, vitamin C, antiviral and antimicrobial agents, and myocardial metabolic agents. CG was treated with captopril (Ningbo Tianheng Pharmaceutical Co., Ltd., GYZZ: H41025659), 12.5 mg/time, 3 times/d, orally after meals, for 1 month. RG patients were treated with creatine phosphate sodium (Beijing Penglai Pharmaceutical Co., Ltd., GYZZ: H20068079) on the basis of captopril treatment. Patients were instructed to rest in bed, with intravenous drip 1 g/time, twice a day, continuous drip for 1 month.

Detection of outcome measures

3 ml of fasting venous blood was collected from both groups on the next morning after admission and centrifuged at a centrifugation radius of 5 cm and a rotation speed of 3,000 r/min for 10 min to separate the upper serum.

1) Myocardial enzyme detection: The levels of aspartate aminotransferase (AST), creatine kinase isoenzyme (CK-MB), creatine kinase (CK), and lactate dehydrogenase (LDH) were measured by enzyme rate method. Beckman

5800 biochemical analyzer with relevant kits was used to detect the above indicators.

2) Cardiac function test: Left ventricular ejection fraction (LVEF), left ventricular fractional shortening (FS), and left ventricular stroke volume (SV) were measured before and after treatment in both groups.

3) Troponin detection: High-sensitivity troponin I (cTnI) and cardiac troponin T (cTnT) were detected by Beckman 5800 biochemical analyzer with relevant kits in the two groups.

4) Detection of inflammatory factors: The levels of tumor necrosis factor-α (TNF-α, mI077385) and interleukin-6 (IL-6, mI058097) were measured in the two groups. The assay was performed by enzyme-linked immunosorbent assay (ELISA) with kits from Shanghai Enzyme Linked Immunosorbent Assay.

Outcome measures

Main outcome measures: Clinical efficacy was compared between the two groups. The changes in myocardial enzyme, cardiac function, troponin and inflammatory factors were observed before and after the treatments.

Secondary outcome measures: Clinical data were compared between the two groups. According to the therapeutic effect, the patients with markedly effective results were considered the significant improvement group, and those with effective or ineffective results were the insignificant improvement group. Risk factors affecting the efficacy of the patients were analyzed by logistic regression analysis, and adverse reactions during the treatments were compared between the two groups.

Efficacy assessment

Criteria for curative effect determination: Significantly effective: original clinical symptoms and signs completely disappeared, heart size, shape, ECG, cardiac function, and myocardial enzymes returned to normal; effective: the clinical symptoms and signs were significantly improved compared with before, and cardiomegaly, ECG, cardiac function and myocardial enzymes were markedly improved but not completely returned to normal; ineffective: clinical symptoms and signs were not significantly improved or even aggravated compared to before treatment. Response rate = (markedly effective + effective)/total number of cases × 100%.

Statistical analysis

The data collected were analyzed by SPSS 20.0 statistical software, in which the measured data were expressed as mean ± standard deviation (Meas ± SD), and the means between the two groups were compared by Student t-test for inter-group comparison and paired t-test for intra-group comparison. χ^2 test was used for rates comparison between the two groups, and logistic regression was to analyze independent risk factors affecting patient outcome. $P < 0.05$ was considered significant.

Results

Clinical data comparison

Comparison of the clinical data between the two groups showed no statistical difference in age, gender, Body Mass Index (BMI), smoking history, alcoholism history, systolic blood pressure, diastolic blood pressure,, or heart rate (all $P > 0.05$, **Table 1**).

Changes in myocardial enzymes

Changes in myocardial enzymes were compared between the two groups. There was no significant difference in AST, CK-MB, CK or LDH between the two groups before treatment (all $P > 0.05$). However, AST, CK-MB, CK, and LDH levels in the two groups after treatment were evidently lower than those before treatment (all $P < 0.001$). In addition, further comparison revealed that such decline was greater in the RG than the CG after treatment (all $P < 0.05$, **Figure 1**).

Cardiac function changes

The cardiac function was compared between the two groups before and after treatment. It was revealed that LVEF, FS, and SV were not statistically different between the two groups before treatment (all $P > 0.05$). However, LVEF, FS, and SV levels increased markedly after treatments in both groups (all $P < 0.001$). In

Table 1. Baseline data comparison

Variable	Control Group (n = 61)	Research Group (n = 79)	X^2/t value	*P* value
Age			3.298	0.069
≥ 30 years	33	48		
< 30 years	28	21		
Gender			0.828	0.362
Male	38	55		
Female	23	24		
BMI			0.306	0.579
≥ 25 kg/m^2	13	20		
< 25 kg/m^2	48	59		
Smoking history			0.828	0.362
Yes	38	55		
No	23	24		
History of alcohol abuse			0.121	0.727
Yes	8	12		
No	53	67		
Systolic blood pressure/mmHg	117.83±18.70	117.21±14.78	0.219	0.826
Diastolic blood pressure/mmHg	74.98±14.97	73.92±14.67	0.419	0.675
Heart rate/(beats·min^{-1})	85.34±17.79	90.05±16.82	1.601	0.112

Note: BMI: Body Mass Index.

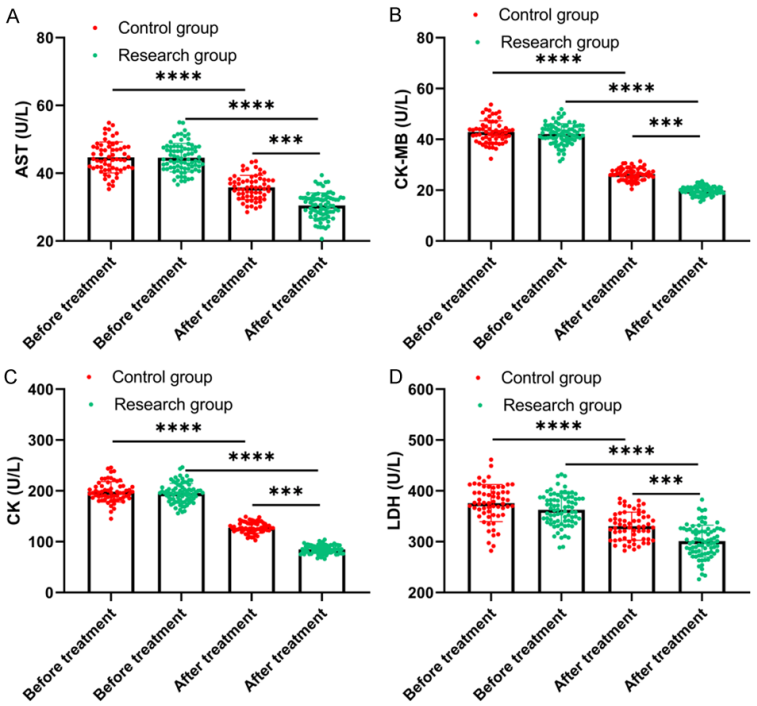

Figure 1. Comparison of myocardial enzyme indexes before and after treatment between the two groups. A. Changes in AST levels before and after treatment. B. Changes in CK-MB levels before and after treatment. C. Changes in CK levels before and after treatment. D. Changes in LDL levels before and after treatment. Note: ***P < 0.001, ****P < 0.0001. AST: Aspartate Aminotransferase; CK-MB: Creatine Kinase Isoenzyme; CK: Creatine Kinase; LDH: Lactate Dehydrogenase.

addition, further comparison revealed that the RG had a greater increase in the above indexes than the CG after treatment (all P < 0.05, **Figure 2**).

Troponin change

The changes in troponin between the two groups were compared. Results showed that there was no significant difference in cTnI and cTnT between the two groups before treatment (both P > 0.05). After the treatments, cTnI and cTnT levels in both groups decreased significantly (both P < 0.001). In addition, further comparison showed that after the treatments, the cTnI and cTnT levels in the RG decreased more significantly than in the CG (P < 0.05, **Figure 3**).

Inflammatory factor changes

Comparing the changes in inflammatory factors between

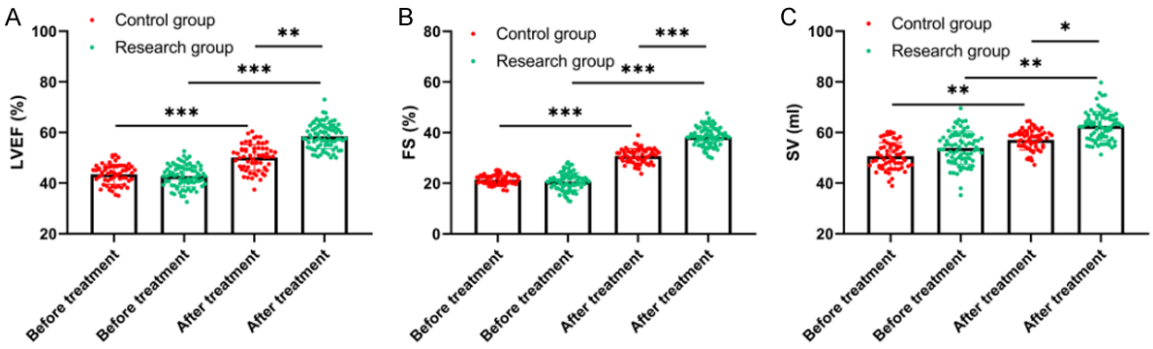

Figure 2. Comparison of changes in cardiac function before and after treatment between two groups. A. Changes in LVEF levels before and after treatment. B. FS level changes before and after treatment. C. Changes in SV levels before and after treatment. Note: *P < 0.05, **P < 0.01, ***P < 0.001. Left Ventricular Ejection Fraction (LVEF), Left Ventricular Fractional Shortening (FS) and Left Ventricular Stroke Volume (SV).

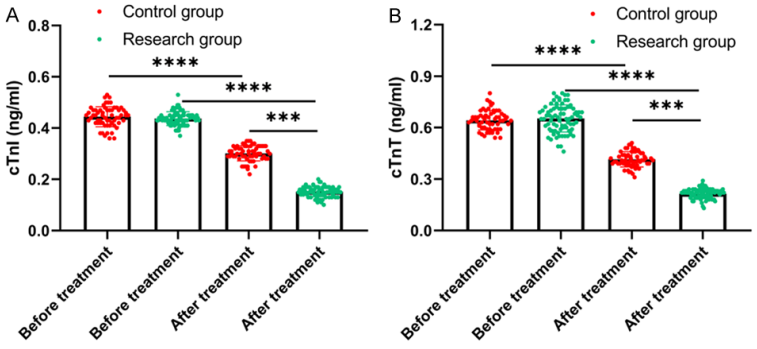

Figure 3. Comparison of changes in troponin before and after treatment between two groups. A. Changes of cTnI levels before and after treatment between two groups. B. Changes of cTnT levels before and after treatment between two groups. Note: ***P < 0.001, ****P < 0.0001. cTnI: High-Sensitivity Troponin I; cTnT: Cardiac Troponin T.

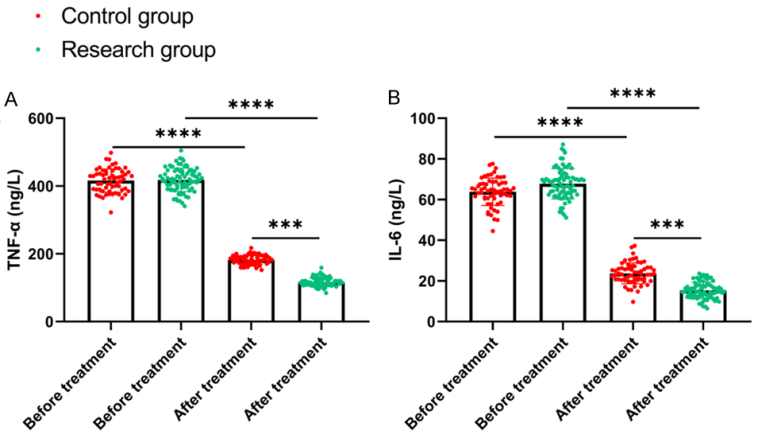

Figure 4. The changes of inflammatory factors before and after treatment in two groups. A. Changes in TNF-α levels before and after treatment between the two groups. B. Changes in IL-6 levels before and after treatment between the two groups. Note: ***P < 0.001, ****P < 0.0001. TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6.

the two groups, the results showed no significant differences in IL- or TNF-α levelsbefore treatment (both P > 0.05). However, after treatment, the average levels of IL-6 and TNF-α were significantly lower than those before treatment (both P < 0.001). Further comparison showed that the declines in the RG were greater than in the CG (both P < 0.05, **Figure 4**).

Efficacy assessment

Evaluation of the efficacy in the two groups after treatment revealed that the overall clinical response rate of the CG was lower than that of the RG (P < 0.05, **Table 2**).

Adverse reaction comparison

Comparison of adverse reactions after treatment between the two groups showed that there were no statistical differences in the incidence of adverse reactions between the two groups (P > 0.05, **Table 3**).

Analysis of risk factors affecting treatment efficacy

According to the clinical efficacy of patients after treatment,

Table 2. Clinical response assessment [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control Group (n = 61)	28 (45.90)	23 (37.70)	10 (16.40)	51 (83.60)
Research Group (n = 79)	43 (54.43)	32 (40.50)	4 (5.07)	75 (94.93)
X^2 value				4.456
P value				0.034

Table 3. Adverse reaction statistics [n (%)]

Group	Headache	Dizziness	Nausea	Somnolence	Incidence rate of adverse reactions
Control Group (n = 61)	2 (3.29)	2 (3.29)	1 (1.64)	3 (4.92)	8 (13.14)
Research Group (n = 79)	3 (3.80)	3 (3.80)	1 (1.26)	2 (2.53)	9 (11.39)
X^2 value					0.095
P value					0.757

Table 4. Univariate analysis

Variable	β	Standard Error	X^2	*P* value	OR value (B)	EXP (B) 95% C.I.	
						Lower limit	Upper limit
Age	0.225	0.343	0.432	0.511	1.253	0.64	2.453
Gender	0.364	0.36	1.027	0.311	1.440	0.711	2.913
BMI	-0.599	0.406	2.183	0.14	0.549	0.248	1.216
Smoking history	0.364	0.36	1.027	0.311	1.440	0.711	2.913
History of alcohol abuse	-0.033	0.483	0.005	0.945	0.967	0.375	2.493
Systolic blood pressure	0.003	0.010	0.085	0.770	1.003	0.983	1.023
Diastolic	0.005	0.012	0.207	0.649	1.005	0.983	1.028
Heart Rate	0.012	0.01	1.457	0.227	1.012	0.993	1.032
AST	-0.024	0.039	0.375	0.540	0.976	0.904	1.054
CK-MB	-0.14	0.045	9.513	0.002	0.870	0.796	0.95
CK	0.011	0.009	1.491	0.222	1.011	0.993	1.029
LDH	0.004	0.005	0.606	0.436	1.004	0.994	1.014
LVEF	0.258	0.054	23.077	< 0.001	1.295	1.165	1.438
FS	0.006	0.06	0.011	0.918	1.006	0.895	1.131
SV	-0.015	0.028	0.284	0.594	0.985	0.934	1.04
cTnI	-14.504	5.645	6.603	0.010	< 0.001	0.000	0.032
cTnT	-10.961	2.857	14.72	< 0.001	< 0.001	0.000	0.005
TNF-α	-0.001	0.005	0.041	0.839	0.999	0.989	1.009
IL-6	0.005	0.023	0.054	0.817	1.005	0.961	1.052

Note: BMI: Body Mass Index; AST: Aspartate Aminotransferase; CK-MB: Creatine Kinase Isoenzyme; CK: Creatine Kinase; LDH: Lactate Dehydrogenase; LVEF: Left Ventricular Ejection Fraction; FS: Left Ventricular Fractional Shortening; SV: Left Ventricular Stroke Volume; cTnI: High-Sensitivity Troponin; cTnT: Cardiac Troponin; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6.

patients with effective improvement were considered the significant improvement group (n = 71), and effective + ineffective resultswere grouped as the insignificant improvement group (n = 69). Further comparison of the factors affecting the efficacy in patients revealed that CK-MB, LVEF, cTnI, and cTnT were risk factors affecting the efficacy in patients (**Table 4**, all P < 0.05). Subsequently, we further determined CK-MB, LVEF, cTnI, and cTnT as independent factors affecting the efficacy in patients by multivariate logistic regression analysis (**Table 5**, all P < 0.05).

Discussion

Viral myocarditis is caused by cardiotropic virus infection with non-specific inflammation of the

Table 5. Multivariate analysis

Variable	β	Standard Error	X^2	*P* value	OR value (B)	95% C.I.	
						Lower limit	Upper limit
CKMB	-0.111	0.050	4.861	0.027	0.895	0.811	0.988
LVEF	0.229	0.058	15.872	< 0.001	1.258	1.123	1.408
cTnI	-13.73	6.258	4.814	0.028	< 0.001	0.000	0.231
cTnT	-7.521	3.146	5.715	0.017	0.001	0.000	0.258

Note: CK-MB: Creatine Kinase Isoenzyme; LVEF: Left Ventricular Ejection Fraction; cTnI: High-Sensitivity Troponin; cTnT: Cardiac Troponin.

myocardium as its main pathologic change. It has predominated as one of the main causes of sudden unexplained death among adolescents in recent years [8]. There are many options for viral myocarditis treatment, yet which one is best remains uncertain.

At present, clinical treatment of viral myocarditis mainly relies on drug therapy [14]. Captopril is an angiotensin-converting enzyme inhibitor that effectively reduces myocardial damage and the production of angiotensin II blocks or reverses myocardial remodeling, and inhibits myocardial inflammatory dilatation [15]. Creatine phosphate is an endogenous high-energy compound that exists in myocardial cells. Exogenous creatine phosphate is a safe, reliable, and effective myocardial cell protector that can directly penetrate the cell membrane, stabilize the phospholipid membrane, keep the high-energy phosphate stable in myocardial cells, and protect myocardial cells from peroxidation damage by reducing oxygen free radicals [16]. Previously, Li et al. [17] examined that gamma globulin combined with phosphocreatine sodium significantly improved the therapeutic effect of patients compared with conventional treatment. In this study, we observed the effects of a combination of two drugs in patients with viral myocarditis. Our results showed that captopril combined with phosphocreatine sodium is more effective than captopril alone, and there is no difference in terms of the incidence of adverse reactions during treatment between the two groups. This shows that the combination of the two can effectively reduce clinical symptoms of patients with favorable therapeutic effect and good safety.

In this study, changes were also detected in cardiac enzymes, cardiac function, troponin, and inflammatory factors. AST, CK-MB, CK, and LDH are the most commonly used indicators to determine myocardial injury, and are widely present in all sorts of cells of the human body. When patients are invaded by external infectious factors, myocardial enzymes are released in large numbers in cardiomyocytes, and CK-MB, CK, and LDH contents in peripheral blood ar abnormally increased [18, 19]. In this study, we found that levels of AST, CK-MB, CK, and LDH in the RG were lower than in the CG after treatment, which indicated that the combined treatment could effectively reduce myocardial injury and effectively protect myocardium. cTnT mostly exists in cardiomyocytes and can be directly involved in myocardial contraction, while cTnI, on the other hand, is present in myocardial tissues and is involved in myocardial contraction and relaxation function. Myocardial damage can cause increased permeability of myocardial cell membranes and induce increased cTnI and cTnT levels [20]. In our results, captopril combined with phosphocreatine sodium could more effectively improve patients' cTnI and cTnT, confirming that the combined treatment can effectively improve myocardial injury. In an early study by Li et al. [21], it was found that troponin, cardiac enzymes, and other indicators in the serum of children with viral myocarditis treated with ulinastatin combined with phosphocreatine sodium were improved, while in our study, those indicators were all improved after treatment, which indicated that captopril combined with phosphocreatine sodium was also effective for viral myocarditis. Due to viral infection of this etiology, myocardial cell lysis, rupture, and necrosis caused by viral infection can lead to massive secretion of various inflammatory factors such as T cell subsets, interleukins, and tumor necrosis factor [22]. For this reason, we further examined the changes in TNF-α and IL-6 in patients before and after treatment, and found that TNF-α and IL-6 in the RG were lower

than those in the CG after treatment. That is to say, the inflammatory response after viral infection was effectively reduced by the combination treatment.

At the end of the study, factors affecting the treatment outcome of patients were identified, and CK-MB, LVEF, cTnI, and cTnT were found to be independent factors affecting patient outcome. CK-MB is highly specific and usually present in skeletal muscle or cardiomyocyte mitochondria. When infected with viruses, cardiomyocytes or skeletal muscle cells get damaged, and CK-MB, which is normally involved in the ATP conversion process inside cells, would flow into the blood, resulting in a significant increase of serum CK-MB. In addition, its concentration is identified to be positively correlated with the patient's condition [23, 24]. Therefore, higher pretreatment CK-MB levels in patients indicate severe disease and lead to unsatisfactory treatment outcomes. Studies have pointed out that patients with severe viral myocarditis have a risk of ventricular remodeling, which is positively correlated with the degree of myocardial injury; while patients with less severe viral myocarditis are identified with no changes in the ventricles and bulbar cavities [25]. Consequently, viral myocarditis patients with lower LVEF normally suffer from more severely impaired cardiac function and more critical condition, and are prone to unsatisfactory therapeutic effect. cTnI and cTnT are contractile proteins present in myofibrils, which mainly regulate the contraction and extension of cardiomyocytes. The cell body structure ruptures when cardiomyocytes are damaged, then this is followed by cTnI and cTnT flowing into human blood through the cell membrane. Higher levels of cTnI and cTnT means more severe damage of myocardial tissue cells, which would cause a worse outcome and a higher risk of ineffective treatment [26]. On account of this, it is recommended to closely observe the changes in CK-MB, cTnI and cTnT, and appropriately combine with other drugs and antibiotics to improve LVEF, as well as the therapeutic effect.

In this study, we determined the therapeutic effect of captopril combined with phosphocreatine sodium in patients with viral myocarditis by retrospective analysis. However, this study has some limitations. First, this study is a retrospective study, so the sample is different from a prospective study. Only existing data were collected and analyzed, and that patients wee not followed up. Second, we have a small sample size of single-center studies in this study. Therefore, we hope to carry out more clinical trials in future studies to improve our conclusions.

In summary, captopril combined with phosphocreatine sodium can reduce the inflammatory response in patients with infectious myocarditis, improving cardiac function and therapeutic effect.

Disclosure of conflict of interest

None.

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