

## Original Research Article

# Efficacy of sodium creatine phosphate in pediatric viral myocarditis and cellular immune functions

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### Abstract

**Purpose:** To investigate the effectiveness of sodium creatine phosphate (SCP) in pediatric viral myocarditis, and cellular immune functions.

**Methods:** Clinical data of 83 children with viral myocarditis admitted to Dezhou Traditional Chinese Medicine Hospital, China between May 2019 and June 2021 were collected and randomly assigned to control (n = 41) and study groups (n = 42). Control group (CNG) received conventional treatment for 14 days, including intravenous drip of sodium fructose diphosphate, vitamin C, and ribavirin, with the addition of prednisone if necessary. Study group (SG) received SCP in addition to conventional treatment for 14 days. Clinical efficacy, cardiac function, inflammatory and immune markers, myocardial injury, and adverse effects at the end of treatment were determined.

**Results:** Results indicated a significantly higher total effective rate in study group (95.24 %) compared to control group (78.05 %) ( $p < 0.05$ ). Study group demonstrated significantly lower heart rates and improved cardiac output, stroke volume, and left ventricular ejection fraction after 14 days of treatment compared to control group ( $p < 0.05$ ). Furthermore, study group exhibited significant reduction in levels of inflammatory markers ( $p < 0.05$ ), enhanced cellular immune markers ( $p < 0.05$ ), and reduced myocardial injury and remodeling markers ( $p < 0.05$ ). Both groups showed similar incidence of adverse reactions.

**Conclusion:** Sodium creatine phosphate (SCP) is effective in treating pediatric viral myocarditis, enhances cardiac function, restores cellular immune function, reduces inflammation, and minimizes myocardial damage and remodeling. There will be need to evaluate the long-term efficacy and prognosis of SCP in treating pediatric viral myocarditis in the future.

**Keywords:** Viral myocarditis, Sodium creatine phosphate, Cardiac function, Cellular immune function, Myocardial remodeling

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## INTRODUCTION

Viral myocarditis is a prevalent cardiomyopathy in clinical pediatrics characterized by myocardial

cell degeneration or necrosis. It is caused by viral invasion of the heart, leading to diffusion or focal inflammatory lesions of the myocardium [1]. Clinical manifestations of the disease include

palpitations, weakness, chest pain, shortness of breath, and other symptoms. Timely treatment and adequate rest during onset of the disease are crucial in preventing the persistence of the disease and subsequent effects on the child's growth and development, including cardiogenic shock and acute myocardial failure [2]. Clinical treatment of pediatric viral myocarditis currently involves antiviral agents, infection inhibition, and myocardial nutrition, but overall efficacy remains sub-optimal, and poor prognosis may result in unsatisfactory cardiac function recovery [3]. Therefore, current effective treatment for pediatric viral myocarditis has gathered worldwide attention.

Sodium creatine phosphate (SCP) is a high-energy phosphate compound used mainly to protect the myocardium during cardiac surgery and to improve metabolic abnormalities of the myocardium in hypoxic conditions [4]. Given the pathological characteristics of pediatric viral myocarditis, including myocardial cell degeneration or necrosis, SCP is hypothesized to be an effective treatment option for the disease. Sodium creatine phosphate (SCP) is applied effectively in the clinical treatment of multiple cardiovascular diseases including chronic heart failure and myocardial infarction [5]. Ma *et al* [6] have found that SCP exhibits a significant therapeutic effect in the treatment of pediatric viral myocarditis by effectively reducing myocardial enzymes and troponin levels and improving the prognosis of the disease. Therefore, this current research was aimed at investigating the efficacy of SCP in pediatric viral myocarditis, and its effects on cardiac and cellular immune function.

## METHODS

### General data

In this retrospective study, clinical data of 83 children admitted to Dezhou Traditional Chinese Medicine Hospital between May 2019 and June 2021 were enrolled and assigned to control and study groups comprising 41 and 42 patients respectively. The research followed the Helsinki Declaration [7] and approval was granted by the Ethics Committee of Dezhou Traditional Chinese Medicine Hospital (approval no. DZSZYY20221206). Guardians of all the patients signed and submitted written informed consents.

### Inclusion criteria

Patients who met the diagnostic criteria of viral myocarditis [8], were between 2 - 12 years of age and had perfect clinical data.

### Exclusion criteria

Patients allergic to therapeutic drugs such as sodium phosphocreatine, use of glucocorticoids and other drugs within 1 month before enrollment, combined congenital heart disease, pericardial effusion, and myocardial infarction, as well as combined serious liver, kidney, and other important organ dysfunction and malignant tumors.

### Treatment

All children included in this study (control and study groups) received conventional treatment for 14 days, which comprised an intravenous drip of 100 mg/kg/day sodium fructose diphosphate (Heilongjiang Jiang Shi Pharmaceutical Co., Ltd., (approval no. H20044931) Harbin, China), an intravenous drip of 150 mg/kg/day vitamin C (Xi'an Yuanda Detian Pharmaceutical Co., Ltd., (approval no. H61023607) Xi'an, China), and an intravenous drip of 15 mg/kg/day ribavirin (Hubei Weishi Biological Pharmaceutical Co., Ltd., (approval no. H19993165) Huangshi, China), with the addition of Prednisone (Xinjiang Yindoland Pharmaceutical Co., Ltd., approval no. H65020151, Urumqi, China) if necessary. Study group received additional intervention with SCP (Shandong Luoxin Pharmaceutical Group Co., Ltd., (approval no. H20183477) Linyi, China), which was administered intravenously at a dosage of 1 g dissolved in 250 mL of 9 % sodium chloride solution (adjusted to 0.5 g for children aged  $\leq 10$  years) Treatment period for both groups was 14 days.

### Evaluation of parameters/indices

#### Clinical efficacy

Clinical efficacy was assessed after treatment and classified as markedly effective (symptoms and signs disappeared or significantly reduced, myocardial enzyme spectrum significantly improved or returned to normal, and ST segment and T-wave (ST-T) changes or electrocardiogram (ECG) arrhythmias disappeared or reduced by over 90 %); effective (symptoms and signs reduced, myocardial enzyme spectrum restored, and abnormal changes in ECG reduced by 50 - 90 %); ineffective (symptoms and signs reduced or progressed, myocardial enzyme spectrum did not improve or deteriorate, and abnormal changes in ECG reduced by less than 50 %). The overall efficacy rate was calculated by summing the markedly effective rate and effective rate [9].

#### Cardiac function

Cardiac ultrasound was used to assess heart rate (HR), cardiac output (CO), stroke volume (SV), and left ventricular ejection fraction (LVEF) before and after 14 days of treatment in both groups [10].

### Inflammatory response

Fasting venous blood (10 mL) was extracted from both groups before and after 14 days of treatment. The collected blood sample was centrifuged at 35 rev/min for 10 min, and the harvested serum was used to measure inflammatory marker levels including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-8, and IL-17 using enzyme-linked immunosorbent assay (ELISA) technique [11].

### Cellular immune function

Flow cytometry was used to detect T-lymphocyte subsets (CD3+, CD4+, CD8+) before and after 14 days of treatment in both groups [12].

### Myocardial injury

Brain natriuretic peptide (BNP), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin T (cTnT) levels were measured before treatment and after 14 days of treatment using an automatic biochemical analyzer [13].

### Myocardial remodeling

The transforming growth factor (TGF)- $\beta$ 1, matrix metalloproteinase (MMP)-9, type I collagen pyridine cross-linked terminal peptide (ICTP), and type I procollagen amino-terminal peptide (PINP) levels were measured using enzyme-linked immunosorbent assay kit (Shanghai Chembond Biotechnology Co., Shanghai, China).

### Adverse effect

Frequency of nausea and vomiting, skin pruritus, and fatigue were recorded for both groups.

### Statistical analysis

Statistical data were analyzed using Statistic Package for Social Science (SPSS) 23.0 software (IBM, Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of the data distribution. Continuous variables with normal distribution, including cardiac function, inflammatory response, cellular immune function, myocardial injury, and myocardial remodeling index, were presented as mean  $\pm$  standard deviation (SD) and analyzed using student t-test. Categorical variables were presented as n (%) and analyzed using Chi-square ( $\chi^2$ ) test.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Baseline information

There were 51 males and 32 females. Mean age was  $6.25 \pm 1.57$  years, and duration of the disease was between 1 – 4 months, with a mean duration of  $2.74 \pm 1.16$  months. There was no significant difference in baseline data of both groups ( $p > 0.05$ ) (Table 1).

### Clinical efficacy

Overall effectiveness rate of study and control group was 95.24 % and 78.05 % respectively. Study group exhibited significantly higher ( $p < 0.05$ ) overall effectiveness rate compared to control group (Table 2).

**Table 1:** Comparison of baseline information between the two groups (mean  $\pm$  SD)

Group	Sex (M/F)	Age (years)	Duration of disease (months)	Body weight (kg)	Type of causative agent (C/CV/EB/RO)
Control (n = 41)	24/17	6.08 $\pm$ 1.65	2.65 $\pm$ 1.38	30.54 $\pm$ 2.84	31/5/3/2
Study (n = 42)	27/15	6.34 $\pm$ 1.56	2.88 $\pm$ 1.42	30.19 $\pm$ 3.15	30/5/4/3

**Note:** C (Coxsackievirus), CV (Cytomegalovirus), EB (EB virus), RO (rotavirus)

**Table 2:** Comparison of clinical efficacy between two groups n (%)

Group	Markedly effective	Effective	Ineffective	Total effective
Control (n = 41)	18(43.90)	14(34.15)	9(21.95)	32(78.05)
Study (n = 42)	24(57.14)	16(38.10)	2(4.76)	40(95.24)
$\chi^2$				5.332
P-value				0.021

**Table 3:** Comparison of cardiac function between the two groups (mean  $\pm$  SD)

Parameter/Group	Before treatment	After treatment
<b>Heart rate (beats/min)</b>		
Control	92.01 $\pm$ 3.45	86.47 $\pm$ 3.04*
Study	91.71 $\pm$ 3.29	80.38 $\pm$ 2.24*#
<b>Cardiac output (mL)</b>		
Control	63.33 $\pm$ 3.45	69.69 $\pm$ 4.02*
Study	63.78 $\pm$ 3.63	78.02 $\pm$ 4.38*#
<b>Stroke volume (L/min)</b>		
Control	3.69 $\pm$ 0.62	5.25 $\pm$ 0.67*
Study	3.85 $\pm$ 0.65	6.75 $\pm$ 0.81*#
<b>Left ventricular ejection fraction LVEF (%)</b>		
Control	42.36 $\pm$ 2.22	52.98 $\pm$ 3.17*
Study	42.71 $\pm$ 2.19	60.29 $\pm$ 4.25*#

Values are presented as mean  $\pm$  SD. \* $P$  < 0.05 vs. same group before treatment, # $p$  < 0.05 vs. control group after 14 days treatment

**Table 4:** Comparison of inflammatory responses between the two groups (mean  $\pm$  SD)

Parameters/Group	Before treatment	After treatment
<b>TNF-<math>\alpha</math> (ng/mL)</b>		
Control	9.56 $\pm$ 1.58	6.25 $\pm$ 1.32*
SG	9.89 $\pm$ 1.67	3.84 $\pm$ 1.18*#
<b>IL-6 (ng/mL)</b>		
Control	63.33 $\pm$ 3.45	69.69 $\pm$ 4.02*
Study	63.78 $\pm$ 3.63	78.02 $\pm$ 4.38*#
<b>IL-8 (ng/mL)</b>		
Control	61.58 $\pm$ 5.62	35.21 $\pm$ 3.67*
Study	62.15 $\pm$ 5.25	24.75 $\pm$ 2.81*#
<b>IL-17 (pg/mL)</b>		
Control	518.65 $\pm$ 85.69	348.5 $\pm$ 38.15*
Study	516.87 $\pm$ 88.42	230.58 $\pm$ 32.58*#

Values are presented as mean  $\pm$  SD. \* $P$  < 0.05 vs. the same group before treatment, # $p$  < 0.05 vs. control group after 14 days of treatment

**Table 5:** Comparison of cellular immune function between the two groups (mean  $\pm$  SD)

Group	CD3+ (%)		CD4+ (%)		CD8+ (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control (n=41)	44.19 $\pm$ 2.49	50.68 $\pm$ 3.53*	32.42 $\pm$ 2.16	36.66 $\pm$ 2.21*	23.08 $\pm$ 1.87	25.41 $\pm$ 1.67*
Study (n=42)	44.56 $\pm$ 2.72	58.71 $\pm$ 4.06*#	32.73 $\pm$ 2.24	41.28 $\pm$ 2.32*#	23.21 $\pm$ 1.96	28.95 $\pm$ 1.91*#

\* $P$  < 0.05 vs. same group before treatment, # $p$  < 0.05 vs. control group after 14 days treatment

### Cardiac function

There was no significant difference in cardiac function before treatment in study and control groups ( $p$  > 0.05). After 14 days of treatment, both groups showed significantly reduced heart rate (HR) and a significant increase in CO (cardiac output), SV (stroke volume), and LVEF (left ventricular ejection fraction) compared with before treatment ( $p$  < 0.05). Also, study group exhibited significantly lower HR and higher CO, SV, and LVEF compared to control group ( $p$  < 0.05) (Table 3).

### Inflammatory response

There was no significant difference in levels of inflammatory response before treatment in both groups ( $p$  > 0.05). However, serum levels of TNF- $\alpha$ , IL-6, IL-8, and IL-17 were significantly reduced in both groups after 14 days of treatment with study group showing lower levels compared to control group ( $p$  < 0.05) (Table 4).

### Cellular immune function

Both groups' pre-treatment indices of cellular immune function did not show any significant differences ( $p$  > 0.05). However, CD3+, CD4+, and CD8+ levels significantly increased in both groups after 14 days of treatment, and higher levels were observed in study group ( $p$  < 0.05) (Table 5).

### Myocardial injury

There was no statistical difference in indices of myocardial injury (BNP, K-MB, LDH and cTnT) before treatment compared in both groups ( $p$  > 0.05). However, BNP, CK-MB, LDH, and cTnT levels were significantly reduced in both groups after 14 days of treatment, and lower levels were observed in study group ( $p$  < 0.05) (Figures 1 A to D).

### Myocardial remodeling

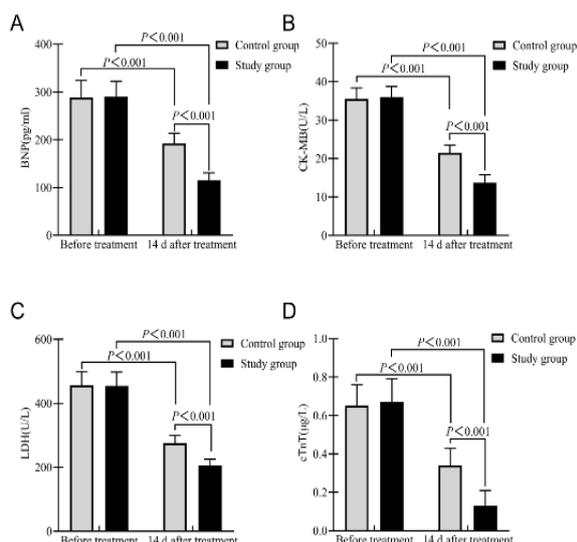
There was no significant difference in TGF- $\beta$ 1, MMP-9, ICTP, and PINP levels before treatment in both groups ( $p$  > 0.05). However, after 14 days of treatment, TGF- $\beta$ 1, MMP-9, ICTP, and PINP levels were significantly reduced in both groups and study group showed even significantly lower levels ( $p$  < 0.05) (Figures 2 A to D).

### Adverse reactions

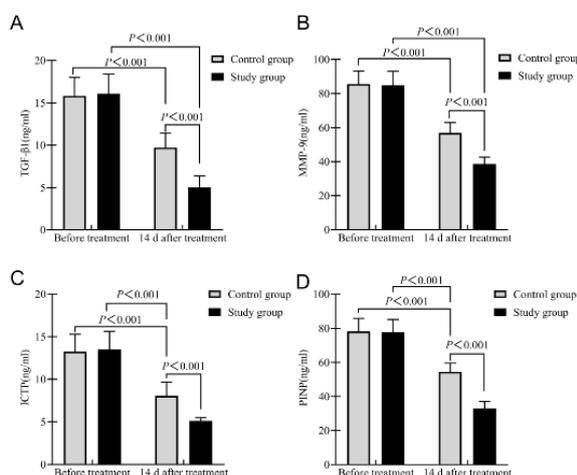
Both groups demonstrated no significant difference in the incidence of adverse reactions ( $p$  > 0.05) (Table 6).

## DISCUSSION

Pediatric viral myocarditis does have some clinical symptoms in the early stage, including



**Figure 1:** Effect of sodium creatine phosphate on myocardial injury in pediatric patients with viral myocarditis. (A, B, C and D) show that the levels of BNP, K-MB, LDH and cTnT respectively were significantly lower in children treated with sodium creatine phosphate for 14 days, and were significantly lower in study group compared to control group ( $p < 0.001$ )



**Figure 2:** Effect of sodium creatine phosphate on myocardial remodeling indices in pediatric patients with viral myocarditis. (A, B, C and D) show that the levels of TGF-β1, MMP-9, ICTP and PINP respectively were significantly lower in children treated with sodium creatine phosphate for 14 days, and were significantly lower in study group compared to control group ( $p < 0.001$ )

vomiting, fever, cough and diarrhea, which is easily ignored. However, as the disease progresses, typical and more serious symptoms such as chest tightness, panic, poor mental health, and in severe cases, respiratory distress, pallor and even sudden death may occur [14]. At present, there are no specific clinical drugs for pediatric viral myocarditis, and treatments such as myocardial nutrition and antivirals are usually used to reduce myocardial damage and relieve symptoms, but the efficacy is not substantial [15]. In this study, sodium creatine phosphate (SCP) was used to treat pediatric viral myocarditis, and the findings revealed a higher overall effective rate in study group (95.24 %) compared to control group (78.05 %). Also, heart rate significantly reduced in both groups after treatment for 14 days, and was significantly lower, while CO, SV, and LVEF were significantly higher in study group.

It is therefore suggested that SCP is an effective treatment approach for pediatric viral myocarditis since it effectively improves cardiac function in children. The reason for this analysis is that the main active ingredient of SCP is phosphocreatine, which plays a pivotal part in muscle energy metabolism and is a reserve of chemical energy for cardiac and skeletal muscle [16].

Sodium creatine phosphate (SCP) promotes recovery of myocardial function by converting adenosine diphosphate to adenosine triphosphate (ATP) in the body and maintaining the stability of cell membranes [17]. Also, SCP effectively inhibits lysyl lipase and reduces oxygen-free radical damage, which in turn improves abnormal myocardial metabolism and promotes recovery of myocardial function. In the past few years, with the deepening of viral myocarditis research, pathological changes have been reported to be related to its impairment of cellular immune function. Conversely, viral infection of cardiomyocytes results in a large number of T lymphocytes infiltrating the myocardium, leading to focal necrosis and myocardial fibrosis [18]. Li *et al* [19] found that children with viral myocarditis exhibited significantly lower immune function than the normal population.

**Table 6:** Comparison of adverse reactions between the two groups n (%)

Group	Nausea and vomiting	Itchy skin	Weakness	Total
Control (n=41)	1(2.44)	1(2.44)	1(2.44)	3(7.32)
Study (n=42)	1(2.38)	1(2.38)	2(4.76)	4(9.52)
$\chi^2$				0.001
P-value				0.974

Viral infection of cardiomyocytes triggers an inflammatory response in addition to direct viral damage, which aggravates myocardial damage and further reduces cardiac function [20]. Kraft *et al* [21] found that serum levels of TNF- $\alpha$ , IL-6, IL-8, and IL-17 were significantly higher in children with viral myocarditis compared to healthy population. The findings of the current research revealed that both groups had lower serum TNF- $\alpha$ , IL-6, IL-8, and IL-17 levels after 14 days of treatment, which were significantly lower in study group. Furthermore, CD3+, CD4+, and CD8+ though significantly higher in both groups were still far higher in study group. It therefore indicated that SCP effectively promotes recovery of cellular immune function in children with viral myocarditis, inhibits inflammatory response, reduces myocardial injury, and promotes physical recovery. Myocardial injury is the main pathological feature of pediatric viral myocarditis, and BNP is mainly secreted after ventricular myocyte damage, which effectively reflects the cardiac function of children [22].

Both CK-MB and LDH are involved in the regulation of myocardial tissue energy metabolism and have high specificity for myocardial injury. When myocardial cells are damaged, CK-MB and LDH concentrations increase significantly. The cTnT serves as a sensitive and specific biomarker for myocardial damage, and it has a high predictive value in the prognosis of children with viral myocarditis [23]. As the disease progresses in children with viral myocarditis, there is a phenomenon of myocardial remodeling during the repair process of damaged myocardial cells, which further reduces cardiac function [24]. During myocardial remodeling, abnormalities in collagen metabolism occur, leading to an elevation in levels of type I collagen catabolic product (ICTP), and the anabolic product (PINP). Also, MMP-9 plays a vital role in the regulation of type I collagen metabolism, while TGF- $\beta$ 1 accelerates the breakdown of collagen metabolism [25].

The finding of this research revealed that after treatment for 14 days, there was a significant decrease in BNP, CK-MB, LDH, cTnT, TGF- $\beta$ 1, MMP-9, ICTP, and PINP levels in both groups, and study group showed a more significant reduction ( $p < 0.05$ ). These findings suggest that SCP effectively inhibits myocardial remodeling, reduces myocardial injury, and promotes recovery of cardiac function in children with viral myocarditis. Furthermore, there was no significant difference in the incidence of adverse effects ( $p > 0.05$ ), indicating that SCP has a good safety profile and this may contribute to compliance of children taking the drug. This

research has therefore contributed valuable insights into the management of viral myocarditis in pediatric patients.

### **Limitations of this study**

The current research has several limitations, including a small sample size, and simple source, and it is only a single-center study, which may lead to some bias in the results. Also, the long-term efficacy and prognosis of SCP in treating pediatric viral myocarditis have not been evaluated and analyzed thus creating the need for further research.

### **CONCLUSION**

Sodium creatine phosphate (SCP) is an effective treatment approach for pediatric viral myocarditis which effectively enhances cardiac function as well as alleviates myocardial injury in children. It promotes the recovery of cellular immune function, reduces inflammatory response, and inhibits myocardial remodeling with a low incidence of adverse effect. There will be the need to evaluate the long-term efficacy and prognosis of SCP in treating pediatric viral myocarditis in the future.

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None provided.

#### **Ethical approval**

None provided.

#### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### **Conflict of Interest**

No conflict of interest associated with this work.

#### **Contribution of Authors**

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this

article will be borne by the authors. Xinhong Liu and Junhua Li contributed equally to this work.

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