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The efficacy observation of ulinastatin combined with creatine phosphate sodium in pediatric viral myocarditis

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Abstract. – OBJECTIVE: This study aimed to compare the efficacy and safety of ulinastatin combined with creatine phosphate sodium and ribavirin combined with creatine phosphate sodium in the treatment of pediatric viral myocarditis.

PATIENTS AND METHODS: 155 children with viral myocarditis in the Xuzhou Children's Hospital, were retrospectively analyzed. 80 of them received ulinastatin combined with creatine phosphate sodium, and were regarded as observation group; other 75 patients received ribavirin combined with creatine phosphate sodium, and were regarded as the control group. The therapeutic efficacy of the two groups was observed, the improvement condition of myocardial enzyme indicator and myocardial troponin I (cTn I) in the two groups were compared before and after the treatment.

RESULTS: The total effective rates of the patients in the observation group and the control group were 93.75% and 76.00%, respectively. The clinical efficacy of the observation group was better than that of the control group ($p<0.05$). The electrocardiogram improvement condition of the observation group was better than that of the control group ($p<0.05$); after the treatment, the expression levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), Creatine Kinase (CK-MB), and cTn I in the observation group were (313.37±9.42) U/L, (29.38±4.97) U/L, (23.67±2.89) U/L, (0.12±0.02) μg/L, respectively. The expression levels of LDH, AST, CK-MB, and cTn I in the control group were (322.43±12.32) U/L, (33.43±5.14) U/L, (26.22±3.37) U/L, (0.24±0.04) μg/L. The levels of myocardial enzyme and cTn I in the observation group and the control group after the treatment were lower than that before the treatment ($p<0.05$), while the level of myocardial enzyme and cTn I in the observation group after the treatment was significantly lower than that in the control group ($p<0.05$).

CONCLUSIONS: The results indicated that, compared with ribavirin combined with creatine phosphate sodium, ulinastatin combined with creatine phosphate sodium had better clinical efficacy in the treatment of pediatric viral myocarditis. It could significantly improve the level of myocardial enzyme indicator and cTn I, and had certain clinical and promotional values and application values.

Key Words:
Ulinastatin, Creatine phosphate sodium, Pediatric viral myocarditis, Myocardial enzyme.

Introduction

Viral myocarditis is an infectious disease caused by a virus or a variety of viruses that conjointly infects heart tissue and causes the occurrence of inflammatory reaction in the myocardium. Its invading virus not only directly damages the myocardium, but also mediates the secondary immune reaction[1]. At the same time, viral myocarditis is also a common pediatric disease. It is often easily recurrent and is usually diagnosed in the late period of the disease due to insufficient clinical manifestations, which is the main cause of pediatric acquired heart failure, cardiomyopathy, and even heart transplantation[2]. In recent years, the morbidity of viral myocarditis has increased year by year, and the mortality of adolescent viral myocarditis reached up to 21%. About 20% of children suffer from sudden death because of viral myocarditis or secondary ventricular arrhythmia. For these reasons, viral myocarditis has seriously threatened the life and health of children who get this disease[3]. Therefore, seeking treatment with better efficacy and high safety is crucial for the prognosis of children with viral myocarditis.

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However, currently there is no specific treatment for this disease in the clinic, and generally, only some heart protection treatments are given, like conventional antiviral, feeding treatment, or inhibition of myocardial oxygen consumption[4]. Ulinastatin is a serum serine protease inhibitor that is widely used to treat various inflammatory diseases and it has been confirmed to have a good cardioprotective effect in experimental animals[5]. Other studies have shown that ulinastatin can alleviate the symptoms of adult viral myocarditis, effectively reduce the prevalence of heart badness, and even have good feedback on the prognosis and survival of patients[6]. Creatine phosphate sodium is a new generation of drugs that improves myocardial energy metabolism, it can store energy in the myocardium, skeletal muscle, and brain tissue, promote the resynthesis of adenosine triphosphate (ATP), reduce myocardial ischemia reperfusion injury, improve cardiac function, and reduce the occurrence of heart disease[7]. It has been widely used in the clinic. In addition, the effect of creatine phosphate sodium has been shown by a large number of clinical practices. It has a good clinical effect on pediatric viral myocarditis and can effectively improve the level of the myocardial enzyme and reduce the occurrence of arrhythmia[8]. It has been proved that ribavirin combined with creatine phosphate is more effective than creatine phosphate alone in the treatment of viral myocarditis in children[9]. However, there are few reports on the treatment of pediatric viral myocarditis with ulinastatin combined with creatine phosphate sodium, and there is still a controversy about the most suitable method for viral myocarditis in children. Thus, in this study, we compared the efficacy of ulinastatin combined with creatine phosphate sodium and ribavirin combined with creatine phosphate sodium in the treatment of pediatric viral myocarditis to provide a clinical reference value for the treatment of pediatric viral myocarditis.

Patients and Methods

Patients

155 children with viral myocarditis in The Xuzhou Children's Hospital, Xuzhou were retrospectively analyzed from January 2018 to January 2019. 80 patients, regarded as the observation group, received ulinastatin combined with creatine phosphate sodium; other 75 patients received ribavirin combined with creatine phosphate sodium, and they were regarded as the control group. In the observation group, there were 60 male children and 20 female children, aged from 2 to 13 years old, and the average age was (8.63±3.76) years old, while there were 56 male children and 19 female children in the control group, aged from 2 to 12 years old, with an average age of (8.54 ±3.15) years old.

The inclusion criteria were: 1) the children with viral myocarditis in the observation group and the control group met the diagnostic criteria of viral myocarditis[10]; 2) the children had cardiac insufficiency and there were significant changes in the electrocardiogram; 3) the level of serum troponin of the children was positive; 4) children's compliance was good.

The exclusion criteria were: 1) the children with dysfunction in lung, brain, liver, and kidney; 2) those who were allergic to medication; 3) the children who had congenital heart disease or (and) secondary cardiac damage.

The content of this study was approved by the Medical Ethics Committee of The Xuzhou Children's Hospital, Xuzhou. The children and/or their family members were informed of the specific operation content of the experiment in details, and they all signed the complete informed consent form.

Treatment Methods

The children in the two groups were given absolute bed rest, routine sedation, oxygen inhalation, antiviral, and other supportive treatments. Electrolyte, coenzyme Q, vitamin C, fructose diphosphate, and other conventional treatment were supplemented[11]. On this basis, the observation group was treated with creatine phosphate sodium (Jilin Yinglian Bio-Pharmaceutical Co., Ltd., H20058621, Jilin, China), 0.5 g/time, which was added into 5% dextrose injection (Qitaihe Pharmaceutical Factory, H20103479, Heilongjiang, China), intravenous infusion, 1 time/d. The children were given ulinastatin (Changzhou Tianpu Pharmaceutical Co., Ltd., H20080367, Jiangsu, China), 0.005 million U/time, and it was added into 100 ml of physiological sodium chloride solution with a concentration of 0.9% (Anhui Shuanghe Pharmaceutical Co., Ltd., H20054037, Anhui, China), intravenous infusion, 3 times/d. The control group was treated with creatine phosphate sodium and ribavirin injection (Zhejiang Chengxin Pharmaceutical Co., Ltd., H20033737, Zhejiang, China) based on routine treatment, and 10 mg/kg was added into 200 mL glucose solu-

tion with a concentration of 5%, intravenous infusion, 1 time/d. The children in the observation group and the control group were continuously treated for 14 days.

Observation Indicators

After the treatment was finished, the physical condition of the children was reviewed, and the clinical signs and the condition of symptom recovery of the children were observed. The electrocardiogram and the level of myocardial enzyme lactate dehydrogenase (LDH), aspartate aminotransferase (AST), Creatine Kinase (CK-MB), and myocardial troponin I (cTn I) were detected and they were compared with those before the treatment. The occurrence condition of adverse reactions was also closely monitored.

The Evaluation Criteria of Efficacy

The clinical efficacy[12] and the improvement condition of the electrocardiogram[13] of the children were compared. The clinical efficacy was divided into: markedly effective - the clinical symptoms and signs of the children both completely disappeared, the electrocardiogram returned to normal, and the level of myocardial enzyme and troponin became normal; effective - the clinical symptoms and signs of the children improved, the electrocardiogram was normal or it shrank before the accidental period, and myocardial enzyme or cTn I significantly improved in the children; ineffective - the clinical symptoms, signs, myocardial enzyme, and cTn I of the children did not significantly improve, and even the illness condition worsened. The total effective rate of the clinical efficacy was markedly effective plus effective.

The improvement condition of the electrocardiogram: markedly effective - the morphological changes of ST-T segment or the condition of arrhythmia of the children significantly reduced or completely disappeared when compared with those before the treatment; effective - the morphological changes of ST-T segment or the condition of arrhythmia of the children decreased by 50% or more than 50% when compared with those before the treatment, but it did not reach the level of markedly effect; ineffective - the decrease of the morphological changes of ST-T segment or the condition of arrhythmia of the children was less than 50% when compared with that before the treatment. The total effective rate of the electrocardiogram improvement condition was markedly effective plus effective.

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 19.0 statistical software (IBM Corp., Armonk, NY, USA) was used to carry out the statistical analysis for the experimental data. All figures were drawn using GraphPad 8 (SOFTHEAD; La Jolla, CA, USA) and the results were checked twice. The enumeration data were expressed in the form of percent. The Chi-square test was used in the comparison between the groups, and the measurement data were expressed in the form of (mean ± standard deviation). The independent sample *t*-test was used in the comparison between groups, and the paired *t*-test was used in the comparison of the indicators within the groups before and after the treatment. $p<0.05$ was considered to be statistically significant.

Results

The Comparison of the General Clinical Data

As shown in Table I, in the observation group there were 53 cases with a history of upper respiratory tract infection, 9 cases with a history of intestinal infection, 3 cases with a history of other infections, and 15 cases without a history of infection. In the control group, there were 50 cases with a history of upper respiratory tract infection, 7 cases with a history of intestinal infection, 4 cases with a history of other infections, and 14 cases without a history of infection. There was no difference when the general data of the children in the observation group were compared with those of the children in the control group ($p<0.05$). The general data included age, weight, gender, previous infection condition, and the level of the myocardial enzyme before the treatment.

The Comparison of the Efficacy

The total effective rates of the treatment of the children in the observation group and the control group were 93.75% and 76.00%, respectively, and the clinical efficacy of the observation group was better than that of the control group ($p<0.05$). The total effective rates of the electrocardiogram improvement condition in the observation group and the control group were 87.50% and 70.67%, respectively, the electrocardiogram improvement condition in the observation group was better than that of the control group ($p<0.05$). See Table II and Table III for details.

Table I. The comparison of the general clinical data ($\bar{x}$±sd) (n%).

Clinical factors	The observation group(n=80)	The control group(n=75)	t/x²	p
Age(year old)	8.63±3.76	8.54±3.15	0.161	0.872
Weight(kg)	32.57±5.63	33.46±5.21	0.310	1.020
The course of disease(month)	6.03±1.53	5.93±1.36	0.429	0.669
Gender			0.002	0.962
Male	60	56		
Female	20	19		
Previous history			0.354	0.950
The history of upper respiratory tract infection	53	50		
The history of intestinal infection	9	7		
The history of other infections	3	4		
The history of infections is none	15	14		
Cardiomegaly			0.997	0.318
Yes	26	22		
No	44	53		
The morphological changes of ST-T segment			0.086	0.769
Yes	53	48		
No	27	27		
The changes of myocardial zymogram			0.365	0.546
Yes	61	54		
No	19	21		
Nodal tachycardia			1.131	0.288
Yes	23	16		
No	57	59		
Before the treatment LDH(U/L)	337.38±15.47	339.87±14.28	1.039	0.300
Before the treatment AST(U/L)	37.38±5.48	36.93±5.64	0.504	0.615
Before the treatment CK-MB(U/L)	30.54±3.48	31.42±3.23	1.629	0.105
Before the treatment cTn I(μg/L)	0.38±0.12	0.35±0.10	1.685	0.094

Table II. The comparison of the efficacy of the children in the observation group and the control group (n%).

Group	The number of case	Markedly effective	Effective	Ineffective	The total effective rate
The observation group(n=80)	80	39 (48.75)	36 (45.00)	6 (7.50)	74 (93.75)
The control group(n=75)	75	28 (37.33)	29 (38.67)	18 (24.00)	57 (76.00)
x^2		2.056	0.638	8.053	8.053
p		0.152	0.425	0.005	0.005

Table III. The comparison of the electrocardiogram improvement conditionof the children in the observation group and the control group (n%).

Group	The number of case	Markedly effective	Effective	Ineffective	The total effective rate
The observation group(n=80)	80	29 (36.25)	41 (51.25)	10 (12.50)	70 (87.50)
The control group(n=75)	75	23 (30.67)	30 (40.00)	22 (29.33)	53 (70.67)
x^2		0.541	1.974	6.695	6.695
p		0.462	0.160	0.010	0.010

The Comparison of the Level of Myocardial Enzyme and cTn I of the Children in the Two Groups

The expression levels of LDH, AST, CK-MB, and cTn I in the observation group after the treatment were (313.37±9.42) U/L, (29.38±4.97) U/L, (23.67±2.89) U/L, (0.12±0.02) μg/L, respectively. The expression levels of LDH, AST, CK-MB, and cTn I in the control group after the treatment were (322.43±12.32) U/L, (33.43±5.14) U/L, (26.22±3.37) U/L, (0.24±0.04) μg/L, respectively. The levels of each myocardial enzyme and cTn I

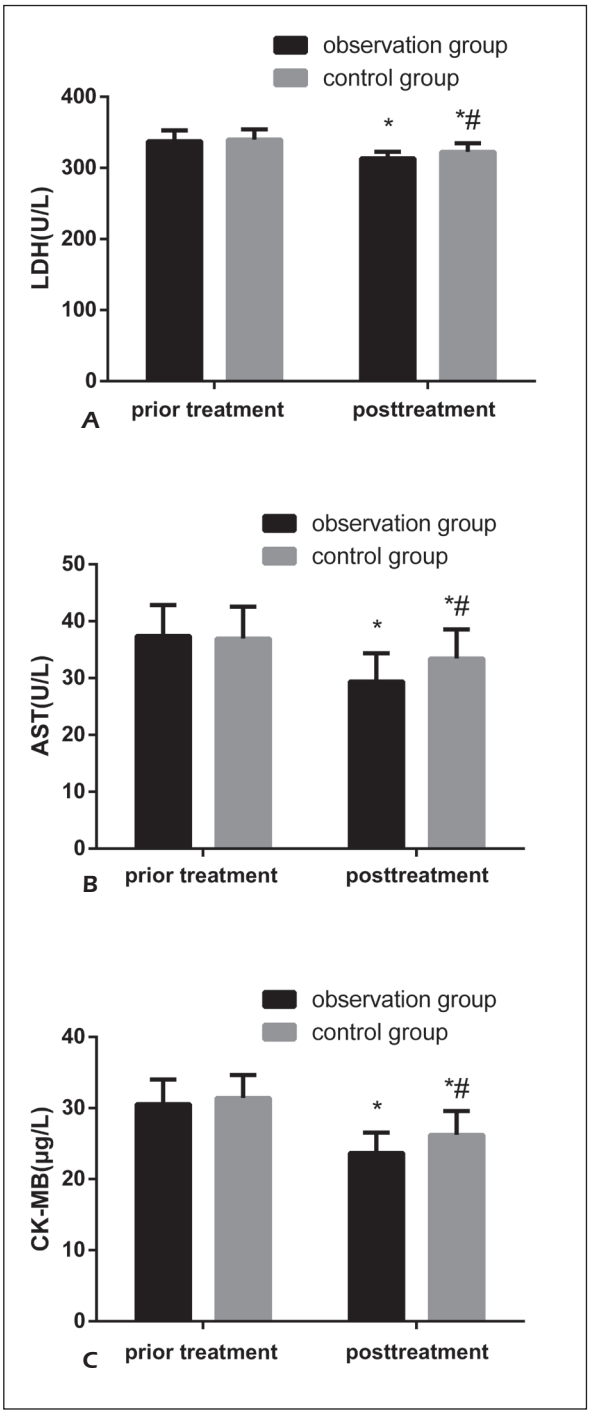

Figure 1. Comparison of myocardial enzymatic function between the observation group and the control group before and after treatment. ***A***, Compared with LDH level before treatment in the same group, $p<0.05$; #compared with the LDH level in the observation group after treatment, $p<0.05$. ***B***, Compared with AST level before treatment in the same group, $p<0.05$; #compared with the AST level in the observation group after treatment, $p<0.05$. ***C***, Compared with CK-MB level before treatment in the same group, $p<0.05$; #compared with the CK-MB level in the observation group after treatment, $p<0.05$.

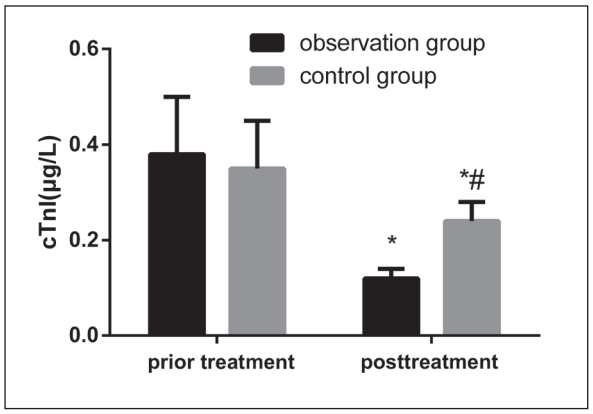

Figure 2. Comparison of cTnI level between the observation group and the control group before and after treatment. *compared with cTnI level before treatment in the same group, $p<0.05$; #compared with the cTnI level in the observation group after treatment, $p<0.05$.

in the observation group and the control group after the treatment were lower than those before the treatment ($p<0.05$), and the levels of each myocardial enzyme and cTn I in the observation group after the treatment were significantly lower than those in the control group ($p<0.05$). Figure 1 and Figure 2 were shown in detail.

The Occurrence Condition of the Adverse Reactions of the Children in the Two Groups

There were no serious adverse reactions in the children in the observation group and the control group during the treatment.

Discussion

Viral myocarditis mainly occurs when Coxsackie virus (CVB3), human herpesvirus 6, and other viruses infect the heart[14]. It can cause a series of heart damage or adverse immune reactions in the human body, resulting in some adverse reactions like the lesion and fibrosis of myocardial cells, and even heart failure, etc[15]. The morbidity of myocarditis in pediatric patients is extremely high, and it seriously threatens the life and health of children. Moreover, it has diverse clinical manifestations in pediatric patients, so timely diagnosis is more difficult[16]. Currently, the clinical treatment is still based on the related supportive treatment, and there are also immunotherapy and a small number of antiviral treatments involved, but they have not shown a specific efficacy[17].

Therefore, finding a new type of treatment is vital for the life and health of children with pediatric viral myocarditis.

Ulinastatin is a protein inhibitor widely used in the treatment of pancreatitis and various inflammations, it has protective effects on the heart. Some studies have shown that ulinastatin is the activating factor of Nrf 2 signal and can facilitate the nuclear translocation and transcription of Nrf 2 and the expression of downstream proteins. It has protective effects on acute viral myocarditis induced by CVB3 virus[5]. Creatine phosphate sodium is a kind of cardioprotective agent with good efficacy, it is often used in heart diseases such as myocardial ischemia, ventricular arrhythmia, and myocardial infarction[18], and it is also a commonly used drug for pediatric viral myocarditis. Currently, some investigations have verified that creatine phosphate sodium has also a cardioprotective effect on pediatric viral myocarditis, which has a better curative effect when combined with other drugs than a single drug in the treatment of viral myocarditis and can improve the level of multiple myocardial enzymes and restore cardiac function[8,19]. However, there are not many reports about the combination use of these two drugs in the treatment of pediatric viral myocarditis, and there is still a controversy about the optimal treatment for viral myocarditis in the clinic. In this study, by comparing the clinical efficacy and myocardial enzyme function of ulinastatin with creatine phosphate sodium and ribavirin with creatine phosphate sodium in the treatment of pediatric viral myocarditis in children, we explored and analyzed the most suitable combined method of creatine phosphate sodium for the treatment of myocardial enzymes. It not only provides a new idea for the treatment of myocarditis, but also explores the effects of ulinastatin combined with creatine phosphate sodium on myocardial enzymes and cTn I, which has important significance in clinical guiding.

The results of this study showed that the total effective rates of the treatment of the children in the observation group and the control group were 93.75% and 76.00%, respectively, while the total effective rates of the electrocardiogram improvement condition were 87.50% and 70.67%, respectively. The clinical efficacy and the electrocardiogram improvement condition of the observation group were better than those of the control group, indicating that ulinastatin combined with creatine phosphate sodium is more effective than ribavirin combined with creatine phosphate sodium in the treatment of viral myocarditis in children. There were no adverse reactions between the two groups, proving that the two methods had high safety for the treatment of viral myocarditis in children, which is also consistent with the results of Schultz et al[9], and can testify the results of this experiment. By further observing myocardial enzymes and cTnI of the two groups, we can learn that the levels of the myocardial enzyme and cTn I in the observation group and the control group after the treatment were lower than those before the treatment, and the levels of myocardial enzyme and cTn I in the observation group were significantly lower than those in the control group. CTnI is an important component of myocardial contractile apparatus with high specificity. The concentration of cTnI in the blood of healthy individuals is almost zero, and it can only be released after myocardial necrosis. The increase of cTnI concentration reflects the damage of myocardial cells. It is the golden standard index for evaluating myocardial injury[20]. The level of cTn I in the study group was lower than that in the control group after treatment, suggesting that ulinastatin combined with creatine phosphate sodium has a stronger protective effect on cardiac function damage in children with viral myocarditis. Wheeler et al[21] compared the efficacy of creatine phosphate sodium treatment and conventional treatment in children with viral myocarditis. They found that creatine phosphate sodium can effectively reduce the activity of myocardial enzymes in children with viral myocarditis and improve the cardiac function of children with viral myocarditis. Its efficacy is better than that of the conventional plan. This is consistent with the result of our study, that is, the use of creatine phosphate sodium can improve the cardiac function of children with viral myocarditis and reduce the level of myocardial enzymes in serum to some extent. Secondly, as above mentioned, ulinastatin has a protective effect on acute viral myocarditis induced by CVB3 virus by activating Nrf2[5]. In addition, studies have shown that ulinastatin can also reduce the leakage of cardiomyocytes in the blood by improving myocardial contractility, thus the level of myocardial enzymes and cTn I will be kept in a range of normal value and the myocardial cells will be protected and be safe from the harm of myocardial ischemia reperfusion injury[22]. Ulinastatin can also regulate autophagy and downregulate the expression of LC3-II by activating the target of rapamycin to reduce the area of myocardial injury and achieve the purpose of protecting myocardial cells[23]. Finally, there are few

reports about the adverse reactions of ulinastatin in the treatment of viral myocarditis in previous literature, but ulinastatin shows high safety in the treatment of severe acute pancreatitis and acute respiratory distress syndrome[24,25]. All the above researches have variously demonstrated that ulinastatin has protective effects on cardiomyocytes, it can effectively improve cardiac function, reduce myocardial injury, and has higher safety. This further supports our viewpoint indicating that, compared with the single use of creatine phosphate sodium, the combined application of ulinastatin and creatine phosphate sodium can better improve the efficacy of pediatric viral myocarditis and is of great significance for the recovery of the cardiac function in children with pediatric viral myocarditis.

However, there are still many shortcomings in this study. Firstly, due to the limitations of the experimental conditions in this study, the sample size is not sufficient, the assessment of the efficacy is not objective enough due to individual differences, and the expansion of the sample size is needed in the later study. Secondly, this study did not deeply investigate the medical mechanism of creatine phosphate sodium and ulinastatin, it is expected that other scholars would supplement and investigate it.

Conclusions

We showed that, compared with ribavirin combined with creatine phosphate sodium, ulinastatin combined with creatine phosphate sodium had better clinical efficacy in the treatment of pediatric viral myocarditis. Moreover, we showed that ulinastatin could significantly improve the level of myocardial enzyme indicator and cTn I, and had certain clinical, promotional, and application value.

Conflict of Interests

The authors declare that they have no conflict of interests.

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