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Original Article

Protective effect of ulinastatin on myocardial injuries in children with severe pneumonia

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Abstract: Background: This study aimed to investigate the effect of ulinastatin on myocardial protection in children with severe pneumonia. Methods: In this retrospective study, children with severe pneumonia were divided into two groups based on their treatment methods. The control group (n=39) received anti-infection therapy, while the experimental group (n=43) received anti-infection therapy combined with ulinastatin. The clinical treatment efficacy, levels of peripheral inflammatory factors, T lymphocyte subsets, QT dispersion and adverse reactions of the two groups were observed and compared before and after treatment. Results: The clinical efficacy was improved after intervention (P<0.05), and the total response rate was 88.4% (38/43) in the experimental group and 64.1% in the control group. The post-treatment levels of interleukin-8 (IL-8), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) in the peripheral blood were lower than those before treatment, with significant differences (P<0.05). After treatment, the serum levels of CD3+, CD4+ and CD4+/CD8+ in the experimental group were significantly higher than those in the control group, whereas the levels of IL-6, IL-8 and hscRP in the peripheral blood were lower in the experimental group than those in the control group, with significant differences (P<0.05). The QT dispersion indexes, such as QTmax, QTmin, QTd, QTcmax, QTcd and QTcmin in the experimental group were shorter than those in the control group (P<0.05). Conclusion: Ulinastatin has significant therapeutic efficacy and safety in the clinical treatment of children with severe pneumonia, which may be related to inhibition of the release of inflammatory factors, shortened QT dispersion and the improvement of immune function of peripheral blood T lymphocyte subsets.

Keyword: Myocardial injuries, T lymphocyte subsets, severe pneumonia, ulinastatin, anti-infection

Introduction

Pneumonia is a common and frequently occurring disease in that occurs in childhood. Worldwide, about 160 million children suffer from pneumonia every year, of which 7%-13% are suffering from severe pneumonia [1]. Every year, about 2 million children under 5 years old die from severe pneumonia [2]. It is an impactful cause of death in children under 5 years old. In China, there are about 20 million children suffering from pneumonia every year, which is first among the four most common diseases seen in children [3].

Clinical research has found that during childhood development, their respiratory system and cardiovascular system do not play an independent role, so they often have hypercapnia and hypoxemia which are found in clinical practice, and even acidosis in severe cases, which causes myocardial damage, affecting the cardiovascular system, and increases the risk of death [4]. Besides, children with severe pneumonia often have cellular immune dysfunction, so the body's ability to resist infection is low [5]. Persistent cellular immune dysfunction can lead to continuous deterioration of disease and multiple organ failure, and affect the prognosis of children. It is clinically significant to improve the immune function of children in a timely manner and reduce the damage of impaired cardiac function to improve the therapeutic effect and prognosis of children with severe pneumonia [6].

Ulinastatin injection is a broad-spectrum protease inhibitor. It is a glycoprotein derived from

the fresh urine of healthy men [7]. It can play a role in preventing the release of various proteases and inflammatory factors, as well as plays a role in anticoagulation, antioxidation, immune regulation, organ protection, etc. [8, 9], and it is an important drug for the clinical treatment of severe pneumonia. Most of the current literature focuses on exploring the effects of ulinastatin on respiratory function, clinical symptom improvement, inflammatory cytokine levels, and lung protection in children with severe pneumonia [10-12]; while there is little research reported on its impact on cellular immune function and cardiac function of these children. Therefore, the aim of this study was to investigate the effect of the ulinastatin on myocardial protection in children with severe pneumonia.

Materials and methods

Study design

This is a retrospective analysis. This study was conducted at Cangxian Hospital from August 2019 to December 2020. Inclusion criteria: 1) children who met the diagnostic criteria of severe pneumonia in Internal Medicine [13], and the diagnosis was confirmed by X-ray film, CT and other imaging examinations; 2) children without injury to heart, liver, kidney and other important organs; 3) children who did not take immunosuppressive drugs recently; 4) children with an age under 18 years old. Exclusion criteria: 1) children with congenital immunodeficiency disease; 2) children with congenital respiratory malformation, congenital pulmonary dysplasia, congenital heart disease or other acute and chronic diseases that can easily cause low immune function; 3) children with severe hepatic and renal dysfunction; 4) children who were treated with immunomodulators or hormones within the most recent 2 weeks; 5) children with malignant tumors or hematological diseases. This study had been reviewed and approved by the medical ethics committee of Cangxian Hospital.

Participants and grouping

In this retrospective study, the data of 82 children with severe pneumonia were analyzed. Among them, 39 children were included in a control group and 43 children in an experimental group.

Interventions

The control group was given routine treatments. Patients were given expectorant, cough relieving, spasmolytic, oxygen inhalation, sedation, nutritional support, and correction of acid-base and electrolyte disorders. Also, 30 mg/(kg/time) of cefoperazone sodium and sulbactam sodium (H20050274, Sinopharm Weiqida Pharmaceutical Co., Ltd) were intravenously injected, 3 times/ for 1 week. Sensitive antibiotics were prescribed according to the drug sensitivity test results. The experimental group was treated with additional intravenous injection of ulinastatin (86449-31-6, Sinopharm Weiqida Pharmaceutical Co., Ltd) 5000 U/kg + 50 ml normal saline (ZK-L0481, Sinopharm Weiqida Pharmaceutical Co., Ltd), once a day for 1 week.

Outcome measures

The primary outcome measures were serum T cell subsets (CD3+, CD4+, CD8+ and CD4+/CD8+) levels and QT dispersion. In the morning, 5 ml of abdominal venous blood was collected from the children and centrifugated to obtain the supernatant. Then, the levels of serum CD3+, CD4+, CD8+ and CD4+/CD8+ were measured with flow cytometry (BD, FACSCANTO II). In addition, a standard 12 lead ECG was performed on the children, and the QT dispersion value was recorded. ECG professionals measured the QT interval in a supine position at baseline, and the horizontal line of Q wave starting point was taken as the measured equipotential line. The related indexes of QT interval (maximum QT interval (QTmax) and minimum QT interval (QTmin)) of 12 lead surface electrocardiogram were measured respectively. Also, the QT interval dispersion (QTd, QTd = QTmax QTmin) was calculated. After heart rate was corrected for according to Bazett formula, the corrected maximum QT interval (QTcmax), corrected minimum QT interval (QTcmin) and corrected QT interval dispersion (QTcd = QTcmax QTcmin) were calculated.

The secondary outcome measures were treatment efficacy and inflammatory factors. The criteria for the evaluation of the total response rate of treatment were as follows, ineffective: the signs and symptoms did not improve or even worsened after treatment; effective: after

Table 1. Comparison of clinical data between the two groups

	Experimental group (n=43)	Control group (n=39)	t/χ^2	*P*
Age (years old)	8.2±1.45	7.15±1.24	2.35	0.43
Sex			7.21	0.22
Male (n%)	23 (53.5%)	27 (69.2%)		
Female (n%)	20 (46.5%)	12 (30.8%)		
Average course of disease	3.52±2.53	3.37±2.35	2.52	0.67
Temperature	39.35±1.14	39.66±0.77	3.39	0.35
Clinical symptoms				
Fever	40 (93.0%)	37 (94.9%)	9.52	0.17
Vomit	13 (30.2%)	11 (28.2%)	7.84	0.09
Convulsions	27 (62.8%)	19 (48.7%)	6.74	0.11
Cough	32 (74.4%)	33 (84.6%)	4.35	0.31
Shortness of breath	13 (30.2%)	16 (41.0%)	3.34	0.27
Pulmonary lesions			3.12	0.13
Unilateral	18 (41.9%)	12 (30.8%)		
Bilateral	25 (58.1%)	27 (69.2%)		

Table 2. Comparison of clinical efficacy between the two groups

	Experimental group (n=43)	Control group (n=39)	χ^2	*P*
Markedly effective	14 (32.6%)	9 (23.1%)	7.268	0.007
Effective	24 (55.8%)	16 (41.0%)	9.737	0.012
Ineffective	5 (11.6%)	14 (35.9%)	4.061	0.003
Total response rate	38 (88.4%)	25 (64.1%)	6.378	0.002
t	4.857	5.732	-	-
P	0.13	0.21	-	-

treatment, the physical signs and symptoms were improved to some extent, but the lung rale was reduced; markedly effective: after treatment, the physical signs and symptoms were significantly improved or disappeared. Total response rate = (total number of cases - cases with ineffective response)/total number of cases × 100%. As for inflammatory factors, the levels of interleukin-8 (IL-8), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) were evaluated to assess the inflammatory changes. Before and after treatment, 3-5 ml of morning fasting venous blood were collected from the children and centrifuged at 3000 R/min for 10 min to obtain the supernatant. The expression of IL-6 (CSB-E04638h, CUSABIO, Wuhan, China), IL-8 (CSB-E04641h, CUSABIO, Wuhan, China) and hsCRP (CSB-E08617h, CUSABIO, Wuhan, China) were detected by enzyme-linked immunosorbent assay. IL-6, IL-8 and hsCRP kits were provided by Everbright Biotechnology Co., Ltd. (CUSABIO, China). The operations were carried out in strict accordance with the instructions.

Statistical analysis

SPSS 24.0 was used for statistical analysis of the data. Measurement data were expressed in ($\chi \pm s$) and subjected to t test. Counting data were expressed in n (%) and processed by χ^2. The difference was statistically significant if $P<0.05$. Graph Pad Prism (Graph Pad Software Inc., CA, USA) was used to illustrate figures.

Results

Clinical characteristics

Table 1 shows the clinical characteristics of the children in two groups (P>0.05). There were 43 children in the experimental group with a mean age of (8.2±1.45) years old, and 39 children in the control group with a mean age of (7.15±1.24) years old. The two groups were comparable in terms of sex, average course of disease, body temperature, clinical symptoms and pulmonary lesions (all P>0.05).

Comparison of clinical efficacy between the two groups

As shown in **Table 2**, the total response rate in the experimental group was 88.4% (38/43), which was significantly higher than 64.1% in the control group (P<0.05).

Comparison of serum levels of inflammatory factors between the two groups

The serum levels of inflammatory factors (IL-6, IL-8 and hsCRP) were obviously lower after treatment in both groups, and the levels in the experimental group were significantly lower

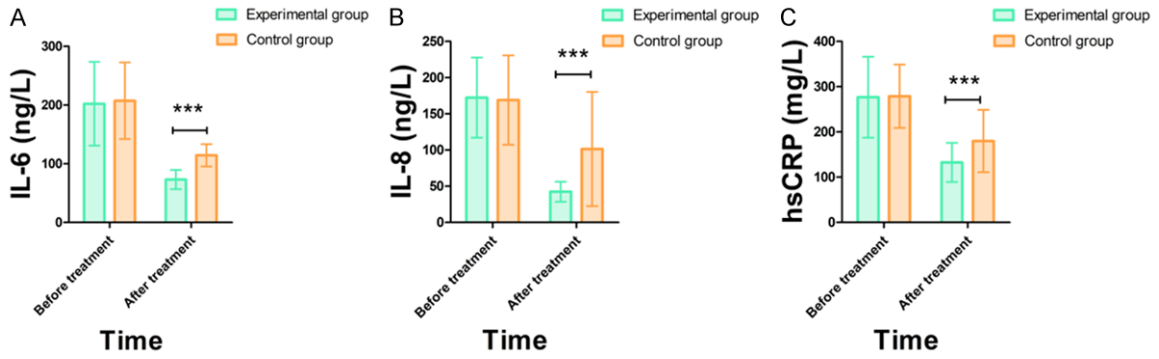


Figure 1. Comparison of serum levels of inflammatory factors between the two groups. A: Comparison of serum levels of IL-6 between the two groups before and after intervention; B: Comparison of serum levels of IL-8 between the two groups before and after intervention; C: Comparison of serum levels of hsCRP between the two groups before and after intervention; Note: Compared with the experimental group, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

than those in the control group after intervention (all P<0.05) (**Figure 1**).

Comparison of T lymphocyte subsets in the peripheral blood between the two groups

There was no significant difference in the levels of peripheral blood CD3+, CD4+, CD8+ and CD4+/CD8+ between the two groups before treatment (P>0.05). After treatment, the levels of peripheral blood CD3+, CD4+ and CD4+/CD8+ in the two groups were significantly increased, and the differences were statistically significant (all P<0.05) (**Figure 2**).

Comparison of QT dispersion between the two groups

The QT dispersion indexes, such as QTmax, QTmin, QTd, QTcmax, QTcd and QTcmin in the experimental group were shorter than those in the control group (all P<0.05) (**Table 4**).

Comparison of adverse reactions between the two groups

There was no statistical significance in the incidence of nausea, vomiting, rash, abdominal pain and diarrhea between two groups after intervention (all P>0.05) (**Table 3**).

Comparison of lung function indexes

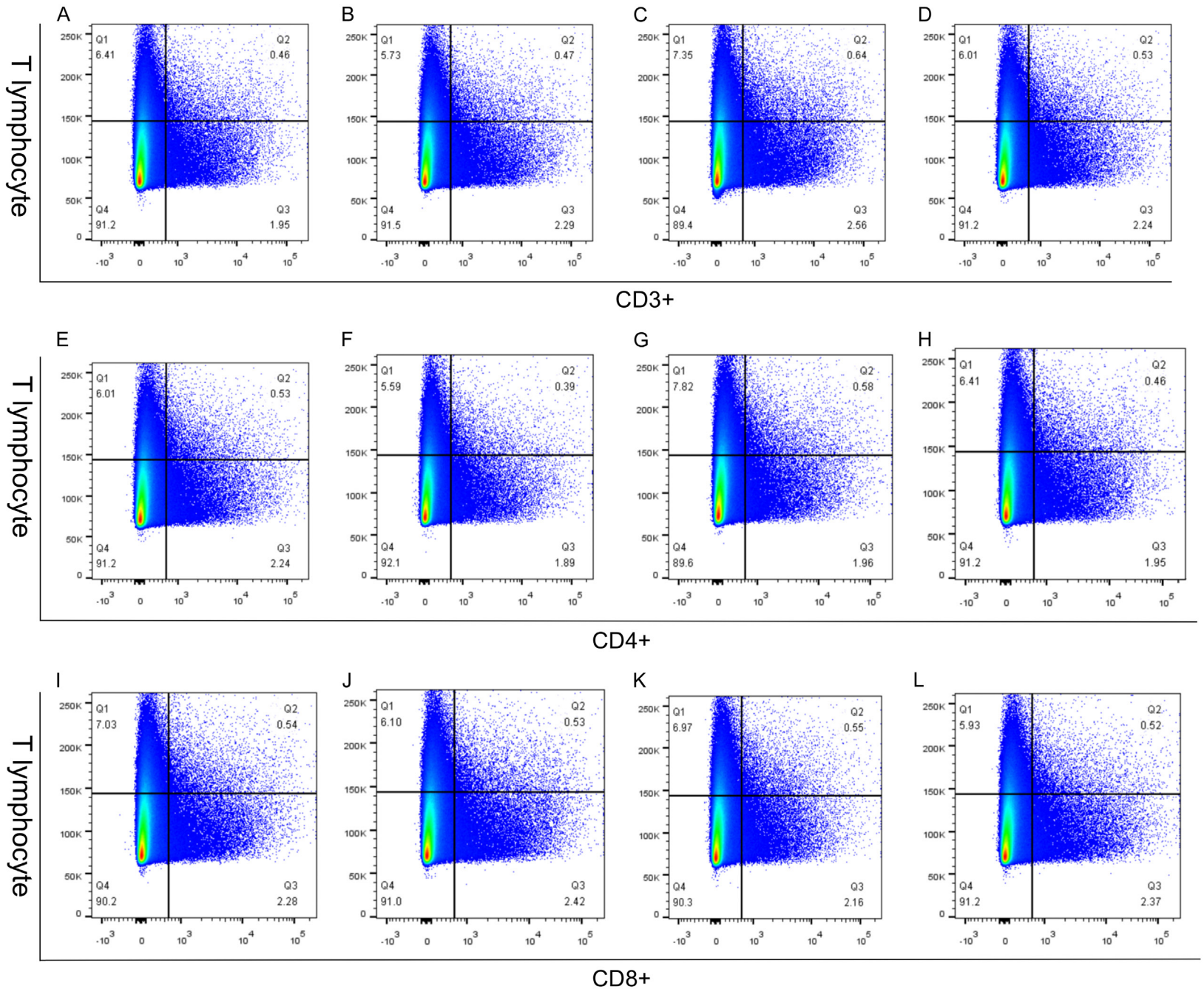
The levels of FEV1, FVC and FEV1/FVC before intervention had no significant difference between the two groups (P>0.05), while after intervention, the lung function improved in the experimental group, and the difference was statistically significant when comparing with that in the control group (P<0.05) (**Table 5**).

Discussion

Severe pneumonia is a common pediatric disease with rapid progress and long treatment time. Because the immune system of children is still in a developmental phase, about 20% of children with severe pneumonia may be complicated with myocardial injury [14]. Severe pneumonia combined with myocardial injury has a higher disability rate and mortality, which seriously affects the growth and development of children and threatens their life [15, 16]. Therefore, early intervention to effectively prevent myocardial injury in children with severe pneumonia is very important to the prognosis.

In our study, we observed that ulinastatin could improve T lymphocyte subsets in children with severe pneumonia. Ulinastatin injection can inhibit the release of IL-6, IL-8 and hsCRP, thereby reducing tissue damage [17-19]. The results of this study showed that the levels of IL-6, IL-8 and hsCRP in the peripheral blood of the two groups after treatment were significantly lower than those before treatment, and the peripheral blood levels of IL-6, IL-8 and hsCRP in the experimental group were significantly lower than those in the control group. It further shows that ulinastatin injection can inhibit the release of inflammatory factors and promote the expression of immunosuppressive factors.

Among T lymphocyte subsets, CD3+ and CD4+ have an immune function, CD8+ can inhibit cel-


A
Q1 6.41
Q2 0.46
Q4 91.2
Q3 1.95
B
Q1 5.73
Q2 0.47
Q4 91.5
Q3 2.29
C
Q1 7.35
Q2 0.64
Q4 89.4
Q3 2.56
D
Q1 6.01
Q2 0.53
Q4 91.2
Q3 2.24
T lymphocyte
CD3+
E
Q1 6.01
Q2 0.53
Q4 91.2
Q3 2.24
F
Q1 5.59
Q2 0.39
Q4 92.1
Q3 1.89
G
Q1 7.82
Q2 0.58
Q4 89.6
Q3 1.96
H
Q1 6.41
Q2 0.46
Q4 91.2
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T lymphocyte
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I
Q1 7.03
Q2 0.54
Q4 90.2
Q3 2.28
J
Q1 6.10
Q2 0.53
Q4 91.0
Q3 2.42
K
Q1 6.97
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Q4 90.3
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L
Q1 5.93
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Q4 91.2
Q3 2.37
T lymphocyte
CD8+

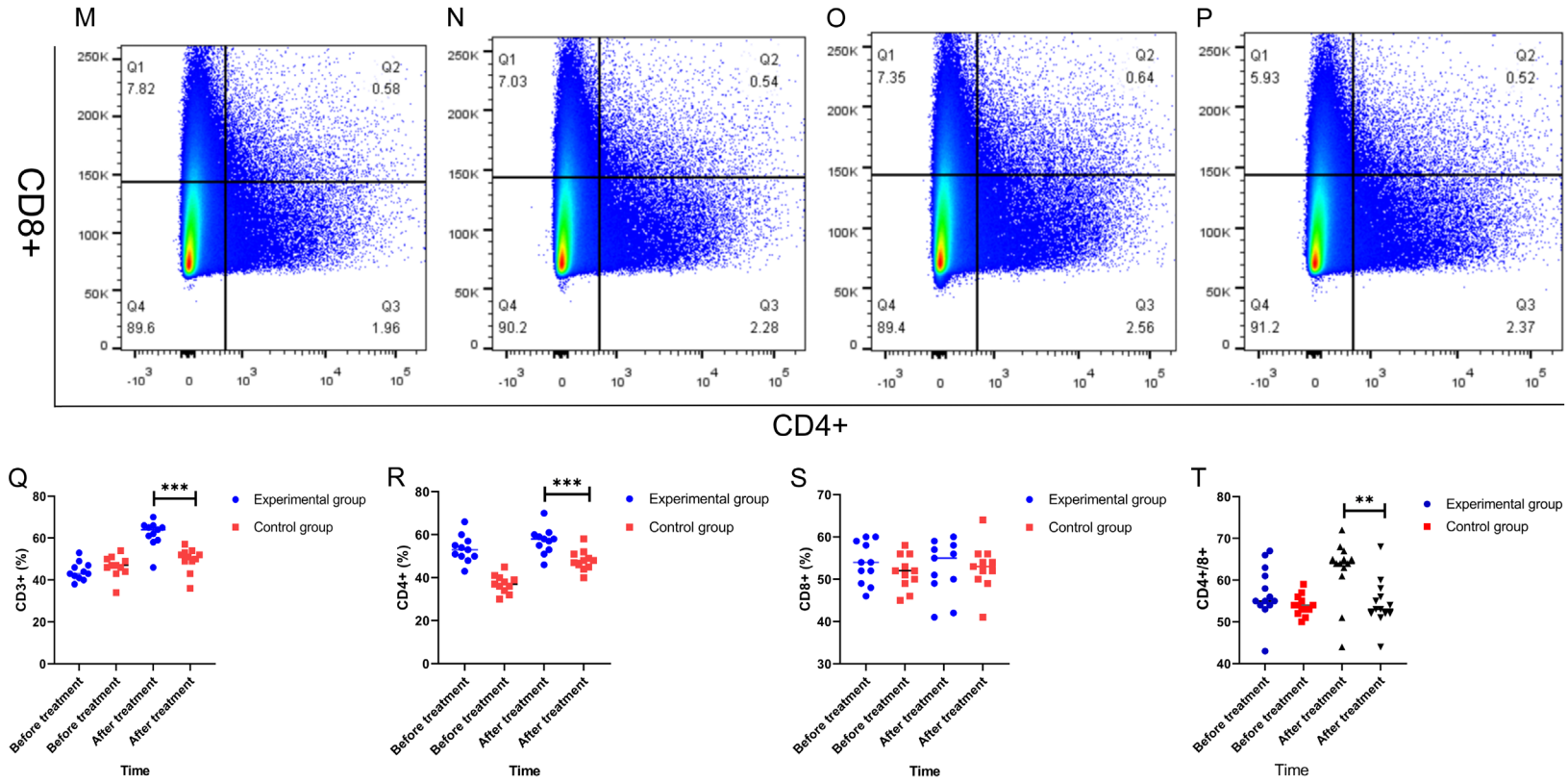

Figure 2. Comparison of T lymphocyte subsets in peripheral blood between the two groups. A-D, Q: Comparison of CD3+ level in peripheral blood between the two groups. E-H, R: Comparison of CD4+ level in peripheral blood between the two groups. I-L, S: Comparison of CD8+ level in peripheral blood between the two groups. M-P, T: Comparison of CD4+/8+ level in peripheral blood between the two groups. *$^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

Table 3. Comparison of adverse reactions between two groups

	Experimental group (n=43)	Control group (n=39)	χ^2	*P*
Nausea	7 (16.3%)	10 (12.8%)	7.153	0.643
Vomit	9 (20.9%)	12 (30.8%)	6.378	0.058
Rash	8 (18.6%)	11 (28.2%)	3.621	0.742
Abdominal pain	14 (32.6%)	13 (33.3%)	4.061	0.051
Diarrhea	5 (11.6%)	3 (7.7%)	9.737	0.382
Total incidence	18 (43.0%)	16 (41.0%)	6.593	0.132

Table 4. Comparison of QT dispersion between the two groups

	Experimental group (n=43)	Control group (n=39)	t	*P*
HR (time/min)	80±9	79±15	-0.273	0.786
QTmax (ms)	381±13	404±22	7.855	<0.001
QTmin (ms)	360±14	371±18	4.027	<0.001
QTd (ms)	20±4	32±8	12.188	<0.001
QTcmax (ms)	438±14	460±25	6.750	<0.001
QTcmin (ms)	414±15	422±24	2.627	0.010
QTcd (ms)	24±5	38±8	13.154	<0.001

lular immune level, CD4+/CD8+ represents the cellular immune state of the body, and CD8+ and CD4+ cells restrict and induce each other in terms of function, forming a specific T lymphocyte network system, so as to maintain and regulate the function of immune defense system [20]. However, the peripheral blood CD3+, CD4+ and CD4+/CD8+ of patients with severe pneumonia were all decreased, so the T lymphocyte subsets of patients with severe pneumonia were disordered, which could lead to abnormal immune function [21, 22]. The results of this study showed that after treatment, the peripheral blood levels of CD3+, CD4+ and CD4+/CD8+ of the two groups were significantly higher after treatment, with statistically significant differences, and the peripheral blood CD8+ level was slightly higher than before treatment, but the difference was insignificant. It showed that the disorder of T lymphocytes in the peripheral blood of the two groups was improved with the prolongation of treatment. The results of this study also showed that the levels of peripheral blood CD3+, CD4+ and CD4+/CD8+ in the experimental group were significantly higher than those in the control group after treatment, and the differences were statistically significant. It shows that the treatment for severe pneumonia with ulinastatin injection on the basis of routine anti-infection treatment can synergistically restore the immune imbalance of patients' peripheral blood T lymphocytes. However, due to the limited sample size and short observation time, this study cannot fully explain the advantages of anti-infection therapy combined with ulinastatin injection in the treatment of severe pneumonia, so it is worth increasing the sample size for further clinical research.

QT interval is the total time course of depolarization and repolarization of myocardial cells, which is equivalent to the end of phase 0 to phase 3 of the action potential. It mainly forms the action potential by changing the transmembrane transport of ions, thus affecting the cardiac electrical activity [23]. QTd is one of the indicators reflecting autonomic nervous function, and also a sensitive indicator reflecting the heterogeneity of myocardial cell electrical activity [24]. Prolonged QTd indicates that the refractory period of cardiac myocytes in different parts is shortened or prolonged, leading to increased repolarization difference of ventricular myocytes, which easily leads to abnormal conduction and reentry, inducing malignant arrhythmia or sudden cardiac death, so it is of great significance in predicting the occurrence of malignant arrhythmia [25]. Some studies have shown that QT variant finger can reflect the difference of repolarization of myocardial cells and is closely related to the autonomic nervous function of children through the analysis of body surface electrocardiogram [26]. Yang et al. [27] and Song et al. [28] reported the predictive role of corrected QT interval (QTc) in OI syndrome. The QT interval and QTc interval in children with OI syndrome were longer than those in the control group, which may be related to autonomic nervous dysfunction. In this study, QTmax, QTmin, QTd, QTcmax, QTcd and QTcmin in the experimental group were shorter than those in the control group, indicating that severe pneumonia resulted in increased vagus nerve excitability in children, obstacles in neural and humoral regulation mechanisms, decreased ventricular contraction amplitude and volume, increased ventricular repolariza-

Table 5. Comparison of lung function indexes between two groups

Index	time	Experimental group (n=43)	Control group (n=39)	t	*P*
FEV1 (L)	Before treatment	1.21±0.48	1.27±0.52	1.128	0.420
	After treatment	3.36±0.48	2.98±0.61	3.213	0.001
	t	4.318	3.316	-	-
	P	0.000	0.000	-	-
FVC (L)	Before treatment	1.57±0.69	1.55±0.67	1.301	0.961
	After treatment	3.97±0.63	2.85±0.58	1.969	0.001
	t	3.228	2.516	-	-
	P	0.000	0.000	-	-
FEV1/FVC (%)	Before treatment	53.94±5.61	54.08±5.62	2.213	0.908
	After treatment	64.43±4.42	59.57±5.51	6.138	0.002
	t	8.718	7.316	-	-
	P	0.000	0.000	-	-

tion difference, increased heart rate, decreased effective circulating blood volume, and transient global cerebral hypoperfusion, leading to syncope. The experimental group had effectively shortened QT interval dispersion after using ulinastatin. This indicated that children treated with anti-infection therapy combined with ulinastatin had significantly improved cardiac function.

Nevertheless, our study has limitations. Firstly, the study population is small because we only enrolled a small number of children. Secondly, we did not investigate the mechanism of action, although the results were promising. Therefore, our results still need further confirmation with larger scale, randomized and control clinical trials.

In summary, ulinastatin has significant clinical efficacy and high safety in the treatment of children with severe pneumonia, which may be related to inhibiting the release of inflammatory factors, ameliorating cardiac function, and improving the immune function of peripheral blood T lymphocyte subsets.

Disclosure of conflict of interest

None.

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