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Original Article

The protective effect of ulinastatin combined with Xuebijing on myocardial injuries in patients with severe pneumonia

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Abstract: Objective: To explore the protective effect of ulinastatin combined with Xuebijing on myocardial injuries in patients with severe pneumonia. Methods: The clinical data of 86 patients with severe pneumonia treated in our hospital were analyzed retrospectively. According to the treatment method each patient was administered, they were divided into a control group (43 cases, routine treatment + Xuebijing) and an observation group (43 cases, routine treatment + Xuebijing + ulinastatin). All the patients were treated for 2 weeks. The clinical efficacy, the inflammatory factor levels (TNF-α, C-reactive protein (CRP), and procalcitonin (PCT)), the myocardial index levels (creatine kinase-myocardial band (CK-MB), lactic dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase (α-HBDE), N-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac troponin I (cTn I)), the blood gas index levels (arterial partial pressure of oxygen (PaO_2), oxygen saturation (SaO_2), and oxygenation index (OI)), the coagulation functions (prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB)) and the acute physiology and chronic health evaluation (APACHE-II) scores were compared between the two groups. Results: After the treatment, the total effective rate in the observation group was higher than it was in the control group ($P<0.05$). After the treatment, the serum TNF-α, CRP, PCT, CK-MB, LDH, α-HBDE, NT-proBNP, and cTnI levels and the APACHE-II scores were decreased in the two groups, and they were even lower in the observation group (all $P<0.05$). The PaO_2, SaO_2, and OI levels were increased in the two groups, and they were higher in the observation group (all $P<0.05$). Compared with before the treatment, the patients' PT and APTT levels in both groups were prolonged after the treatment, and the observation group was longer than the control group. The plasma FIB levels were decreased in both groups, and they were lower in the observation group than in the control group ($P<0.05$). Conclusion: Ulinastatin combined with Xuebijing can significantly alleviate pulmonary inflammation, improve the blood gas, and protect the damaged myocardia in patients with severe pneumonia.

Keywords: Severe pneumonia, ulinastatin, Xuebijing, myocardial injury, blood gas

Introduction

Severe pneumonia is a serious type of pneumonia, and it can easily develop in patients of all ages. The main treatment is to promptly control the progression of the inflammation. However, if the inflammation is not well controlled, it can lead to life-threatening complications, such as heart failure [1]. Myocardial injuries are one of the common complications of severe pneumonia. Some studies have revealed that more than half of patients with severe pneumonia may also suffer from varying degrees of myocardial injury [2]. Therefore, the medical staff should also pay attention to protecting the damaged myocardium, promptly reversing the myocardial injury and improving the cardiac function of patients in addition to controlling the progression of the inflammation during the clinical treatment, which is conducive to improving patient prognosis.

Xuebijing injections can enhance the immune function of the body and reduce the blood's

hypercoagulable state. At present, there are many studies on using Xuebijing injections to treat septicopyemia and severe pneumonia, but studies on using Xuebijing for the myocardial protection of patients are extremely rare [3, 4]. Ulinastatin is a protease inhibitor with a variety of biological activities, such as anti-inflammatory and anti-oxidative activities, etc. It is widely used in septicopyemia, acute pancreatitis, and pneumonia, and it has significant anti-inflammatory effects. Meng et al. have shown that ulinastatin can significantly improve the inflammatory states of sepsis patients, but there is seldom research about its influence on the cardiac function [5]. It is not known whether ulinastatin combined with Xuebijing can improve the damaged cardiac function of patients with severe pneumonia. Therefore, this study was mainly designed to investigate the effect of the combination of the two on myocardial protection in patients with severe pneumonia.

Materials and methods

Baseline data

The clinical data of 86 patients with severe pneumonia treated in our hospital from December 2018 to February 2020 were analyzed retrospectively. According to different treatment methods, they were divided into an observation group and a control group, with 43 cases in each group. In both groups, the patients underwent routine treatment for severe pneumonia after admission. In the control group, the patients were administered an intravenous drip of Xuebijing. In the observation group, the patients were treated with ulinastatin combined with Xuebijing.

Inclusion criteria: (1) Patients aged 25 to 70 years. (2) Patients who had a large amount of purulent discharge in their lungs. (3) Patients whose chest CTs showed patchy or cloudy shadows in both lungs. (4) Patients who met the documented diagnostic criteria for severe pneumonia and who were diagnosed with severe pneumonia through various clinical examinations [6]. (5) Before admission, the patients' myocardial enzyme spectrum and myocardial injury-related indicators (such as NT-probNP) were abnormal.

Exclusion criteria: (1) Patients who had a history of myocardial infarction treatment during the six months before their admission. (2) Patients with heart, liver, kidney, or other organ dysfunction. (3) Patients with malignant tumors, etc. (4) Patients with autoimmune diseases or mental diseases; (5) Women in a special physiological period. (6) Patients who were allergic to the drugs in this study.

All the patients signed informed consent, and this study was approved by the ethics committee of our hospital (approval No. 20180210001).

Methods

After admission, the patients in both groups were administered routine treatment for severe pneumonia, such as mechanical ventilation, antibiotics, cough suppressant, and resolving phlegm. In the control group, the patients underwent an intravenous drip of Xuebijing (Tianjin HongRi Pharmaceutical Co., Ltd., Z20040033, specification: 10 mL), 100 mL/time; The infusion was completed within 30 to 40 min, once a day. In the observation group, the patients were treated with ulinastatin combined with Xuebijing, and the administration of the Xuebijing was the same as it was in the control group. The ulinastatin (200,000 U) (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., H20040506, 2 ml:100,000 U) was dissolved in 500 mL of 5% glucose (Shanghai Changzheng Fumin Jinshan Pharmaceutical Co., Ltd., H31022226, specification: 500 mL:25 g) or 0.9% sodium chloride (Shanghai Changzheng Fumin Jinshan Pharmaceutical Co., Ltd., H31021918, specification: 500 mL:4.5 g) for the intravenous infusion, and the infusion was completed within 1.5 to 2 h, once a day. All the patients were treated consecutively for 14 days.

Outcome measures

The main outcome measures: (1) According to the medical literature, the clinical effect was evaluated after the treatment [6]. Markedly effective: symptoms such as dyspnea and chest inflammation disappeared completely or improved significantly, and the arterial blood gas and body temperatures returned to normal. Effective: the symptoms such as dyspnea improved, the scope of the chest inflammation decreased, and the arterial blood gas indicators improved. Ineffective: The patients still had serious symptoms. Total effective rate = (markedly effective + effective) cases/total cases

Table 1. The baseline information of the two groups ($\bar{x}\pm sd$)

	Observation group (n=43)	Control group (n=43)	χ^2/t	P
Gender (n)			1.165	0.280
Male	20	25		
Female	23	18		
Age (year)	47.5±4.9	48.3±5.3	0.727	0.469
BMI (kg/m^2)	23.20±2.88	22.15±2.94	1.673	0.098
Breathing rate (times/min)	45.4±4.9	45.2±6.3	0.164	0.870
PaO_2 (mmHg)	56.48±5.22	57.20±5.55	0.620	0.537
OI	223.30±17.79	224.49±17.38	0.314	0.754
Complications (n)			0.924	0.630
Hypertension	5	7		
Hyperlipidemia	2	4		
Diabetes	2	1		

Note: PaO_2: arterial partial pressure of oxygen; OI: oxygenation index.

Table 2. The clinical efficacy after the treatment in both groups [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effective rate
Observation group (n=43)	15 (34.88)	24 (55.81)	4 (9.30)	39 (90.70)^b
Control group (n=43)	12 (27.91)	20 (46.51)	11 (25.58)	32 (74.42)
χ^2				3.957
P				0.047

Note: Compared with the control group, ^{b}P<0.05.

×100%. (2) Approximately 5 mL of venous blood was drawn from the patients before and after the treatment, and the serum was separated using centrifugation. The tumor necrosis factor (TNF-α), C-reactive protein (CRP). and procalcitonin (PCT) levels were measured using ELISA. All the kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., and the batch numbers were ml077385, ml057570, and ml026011, respectively. (3) The creatine kinase-myocardial band (CK-MB), lactic dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase (α-HBDE), N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) levels were measured using an automatic biochemical analyzer.

Secondary outcome measures: (1) Approximately 3 ml of blood was drawn from the radial artery or femoral artery of each patient before and after the treatment. The arterial partial pressure of oxygen (PaO_2) and the oxygen saturation (SaO_2) levels were measured using a blood gas analyzer, and the oxygenation index (OI) was calculated ($OI=PaO_2/FiO_2$). (2) Before and after the treatment, about 5 mL of venous blood was drawn, and the plasma was centrifuged. The plasma prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen (FIB) levels were measured using an automatic coagulation analyzer. (3) The acute physiology and chronic health evaluation (APACHE-II) scores were used to evaluate the prognosis, including the acute physiology scores (APS, 60 points), the age score (6 points), and the chronic health evaluation scores (CPS, 5 points) [7]. APACHE-II had a total possible score of 71 points, and the lower the score, the better the prognosis.

Statistical analysis

SPSS 20.0 was used for the data analysis. The count data were expressed as n (%), and χ^2 tests were used. The measurement data were presented as $\bar{x}\pm sd$. Paired t tests were used for the comparisons before and after the treatment. Independent t tests were used for the comparisons between the two groups. A difference was statistically significant when P<0.05.

Results

Baseline data

There was no significant difference in baseline data between the two groups (all P>0.05), so they were comparable (**Table 1**).

Clinical efficacy

The total effective rate of the patients in the observation group was higher than it was in the patients in the control group after the treatment (P<0.05, **Table 2**).

Inflammatory factors

There was no statistically significant difference in the serum TNF-α, CRP, or PCT levels between the two groups before the treatment

Table 3. The serum inflammatory factor levels before and after the treatment in both groups ($\bar{x}$±sd)

Index	Time	Observation group (n=43)	Control group (n=43)	*t*	*P*
TNF-α (ng/L)	Before treatment	194.49±15.40	193.78±13.70	0.226	0.822
	After treatment	65.57±9.22[a]	96.44±10.88[a]	14.194	<0.001
CRP (mg/L)	Before treatment	83.30±7.27	82.89±6.57	0.274	0.784
	After treatment	23.40±4.30[a]	31.10±5.21[a]	7.474	<0.001
PCT (ng/mL)	Before treatment	2.96±0.53	2.80±0.59	1.323	0.189
	After treatment	0.94±0.30[a]	1.37±0.33[a]	6.322	<0.001

Note: TNF-α: tumor necrosis factor; CRP: C-reactive protein; PCT: procalcitonin. Compared with pre-treatment, [a]P<0.05.

Table 4. The indicator levels related to myocardial injury before and after the treatment in both groups ($\bar{x}$±sd)

Indicator	Time	Observation group (n=43)	Control group (n=43)	*t*	*P*
CK-MB (U/L)	Before treatment	387.58±19.95	388.75±18.85	0.280	0.781
	After treatment	114.49±15.44[a]	148.47±16.67[a]	9.806	<0.001
LDH (U/L)	Before treatment	598.58±23.38	600.18±25.59	0.303	0.763
	After treatment	304.49±20.05[a]	375.59±23.36[a]	15.145	<0.001
α-HBDE (U/L)	Before treatment	330.03±20.02	331.18±19.75	0.268	0.789
	After treatment	102.28±12.22[a]	147.47±17.60[a]	13.830	<0.001
NT-proBNP (pg/mL)	Before treatment	390.04±18.44	389.78±17.09	0.068	0.946
	After treatment	226.38±12.20[a]	275.57±14.95[a]	16.716	<0.001
cTnI (μg/L)	Before treatment	2.88±0.84	2.94±0.93	0.314	0.754
	After treatment	1.25±0.30[a]	1.87±0.38[a]	8.397	<0.001

Note: CK-MB: creatine kinase-myocardial band; LDH: lactic dehydrogenase; α-HBDE: α-hydroxybutyrate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; cTnI: cardiac troponin I. Compared with before the treatment, [a]P<0.05.

(all P>0.05). After the treatment, the serum TNF-α, CRP, and PCT levels were decreased in both groups, and they were even lower in the observation group (all P<0.05, **Table 3**).

Related indicators of myocardial injury

There was no statistically significant difference in the serum CK-MB, LDH, α-HBDE, NT-proBNP, or cTnI levels between the two groups before the treatment (all P>0.05). After the treatment, the serum levels of the above indexes were decreased in both groups, and they were even lower in the observation group (all P<0.05, **Table 4**).

Blood gas analysis

There was no statistically significant difference in the PaO_2, SaO_2 or OI levels between the two groups before the treatment (all P>0.05). After the treatment, the PaO_2, SaO_2 and OI levels were increased in the two groups, and they were higher in the observation group (all P< 0.05, **Table 5**).

Coagulation function

Compared with before the treatment, the PT and APTT of the patients in both groups were prolonged after the treatment, and the observation group was longer than the control group. The levels of plasma FIB were decreased in both groups, and they were lower in the observation group than they were in the control group (all P<0.05, **Table 6**).

APACHE-II scores

There was no statistically significant difference in the APACHE-II scores between the two groups before the treatment (all P>0.05). After the treatment, the APACHE-II scores were declined in both groups, and they were even lower in the observation group (all P<0.05) (**Figure 1**).

Discussion

Severe pneumonia is a very dangerous disease, and it progresses rapidly. If the body's inflammation control effect is poor, it can induce a

Table 5. The blood gas analysis before and after the treatment in both groups ($\bar{x}$±sd)

Index	Time	Observation group (n=43)	Control group (n=43)	*t*	*P*
PaO_2 (mmHg)	Before treatment	56.48±5.22	57.20±5.55	0.620	0.537
	After treatment	95.11±4.94[a]	83.22±4.87[a]	11.240	<0.001
SaO_2 (%)	Before treatment	85.33±4.64	85.84±3.84	0.555	0.580
	After treatment	98.87±1.13[a]	94.03±2.77[a]	10.609	<0.001
OI	Before treatment	223.30±17.79	224.49±17.38	0.314	0.754
	After treatment	334.30±16.37[a]	298.88±15.50[a]	10.303	<0.001

Note: PaO_2: arterial partial pressure of oxygen; SaO_2: blood oxygen saturation; OI: oxygenation index. Compared with before the treatment, [a]P<0.05.

Table 6. Comparison of the coagulation function between the two groups before and after the treatment (score, $\bar{x}$±sd)

Index	Time	Observation group (n=43)	Control group (n=43)	*t*	*P*
PT (s)	Before treatment	13.82±2.94	13.77±2.28	0.088	0.930
	After treatment	16.03±2.16	14.76±1.03	3.480	<0.001
APTT (s)	Before treatment	33.30±3.29	33.64±2.94	0.505	0.615
	After treatment	38.89±2.04	35.87±2.10	6.764	<0.001
FIB (g/L)	Before treatment	4.40±0.94	4.45±0.89	0.253	0.801
	After treatment	3.20±0.79	3.77±0.71	3.519	<0.001

Note: PT: prothrombin time; APTT: activated partial thromboplastin time; FIB: fibrinogen.

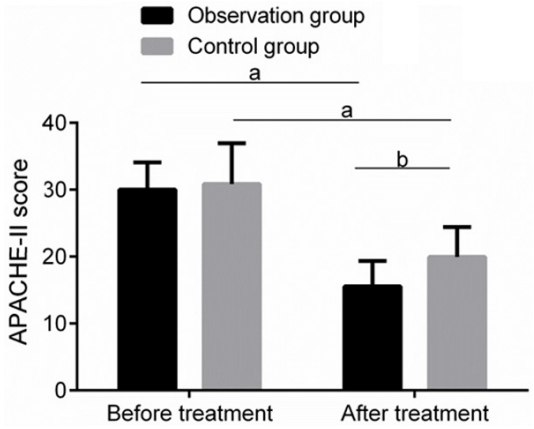

Figure 1. A comparison of the APACHE-II scores before and after the treatment between the two groups. Note: APACHE-II: Acute physiology and chronic health status score. Compared with before the treatment, [a]P<0.05; compared with the control group, [b]P<0.05.

systemic inflammatory reaction, which eventually leads to the patient's death due to various complications [8]. Among them, heart failure caused by myocardial injury is the main cause of death [9, 10]. Therefore, the damaged myocardium should be protected during the treatment of severe pneumonia.

Xuebijing is a Chinese patent medicine for promoting blood circulation and removing blood stasis. Basic research shows that Xuebijing can also inhibit the release of the inflammatory mediators and improve the microcirculation of the body [11, 12]. Ulinastatin is a broad-spectrum trypsin inhibitor that can stabilize the lysosomal membrane after binding with the cell membrane receptor, inhibiting the inflammatory factors such as neutrophils to release inflammatory mediators, and effectively improving the inflammatory state of the body [13]. In this study, they were used to treat severe pneumonia. The results showed that the total effective rate in the observation group was higher than it was in the control group, and the serum TNF-α, CRP, and PCT levels were lower than the corresponding levels in the control group after the treatment, suggesting that ulinastatin combined with Xuebijing can significantly alleviate the inflammatory state of patients with severe pneumonia and improve the overall clinical effectiveness. Zhang et al. demonstrated that ulinastatin combined with Xuebijing can significantly inhibit pulmonary inflammation and improve pulmonary function in patients with pneumonia [14].

More than half of the patients with severe pneumonia may also suffer from varying degrees of myocardial injury, which is also the main factor that induces heart failure and leads

to patient death [15]. The monitoring of myocardial zymogram can directly reflect the degree of myocardial injury [16, 17]; the serum NT-proBNP, and cTnI levels are clinically recognized markers of myocardial injury [18, 19]. Ulinastatin can stabilize the lysosomal membrane which can produce myocardial inhibitors after binding to the binding sites of various enzymes in the body, such as plasmin and neutrophil elastase, thus protecting the damaged myocardium [20, 21]. In this study, the serum CK-MB, LDH, α-HBDE, NT-proBNP, and cTnI levels in the observation group were lower than they were in the control group after the treatment, which suggests that ulinastatin combined with Xuebijing has more significant protective effects on the damaged myocardial cells in patients with severe pneumonia.

Patients with severe pneumonia suffer severe pulmonary function decline, pulmonary ventilation dysfunction, and the blocked exchange of CO_2 and O_2, which can easily lead to hypercapnia, and can even result in metabolic acidosis in severe cases, so it is extremely detrimental to patient prognosis [22]. It is reported that patients with severe infection often also have abnormal coagulation function, and the coagulation-related indicators can be used to indicate the severity of the infection [23]. In this study, the PaO_2, SaO_2 and OI levels in the observation group were higher than they were in the control group after the treatment, and the PT and APTT were longer than they were in the control group, while the plasma FIB levels and the APACHE-II scores were all lower than they were in the control group, suggesting that ulinastatin combined with Xuebijing can significantly improve the coagulation function, the blood gas index levels, and the prognoses of patients with severe pneumonia, which is consistent with the research results of Hui et al. [24].

However, this was a single center clinical study with a limited sample size. Moreover, this study was designed to only compare the changes in the myocardial-related indicators before and after the treatment, and the patients were not followed up for a long time. The effect of ulinastatin combined with Xuebijing on the long-term myocardia of patients with severe pneumonia still needs to be confirmed by more in-depth research.

To sum up, ulinastatin combined with Xuebijing can significantly alleviate pulmonary inflammation, improve the blood gas, and protect the damaged myocardia in patients with severe pneumonia.

Disclosure of conflict of interest

None.

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