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Effect of ulinastatin on vasoactive substances, oxidative stress and inflammatory response in patients with acute exacerbation of COPD

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ABSTRACT

Objective: To study the effect of ulinastatin on vasoactive substances, oxidative stress and inflammatory response in patients with acute exacerbation of COPD. **Methods:** Patients with acute exacerbation of COPD who were treated in Chengdu Fifth People's Hospital between August 2013 and July 2016 were selected as the research subjects and randomly divided into ulinastatin group and normal control group who received ulinastatin combined with conventional therapy and conventional therapy respectively. The serum contents of vasoactive substances, stress response hormones, oxidative stress products and inflammatory response mediators were detected before treatment and 7 d after treatment. **Results:** 7 d after treatment, serum D-D, AT-II, pro-BNP, ACTH, FC, NE, MDA, 8-iso-PG, HSP27, HSP70, PCT, CRP, CCL18 and MSP contents of both groups of patients were significantly lower than those before treatment while TT3 and TT4 contents were significantly higher than those before treatment; serum D-D, AT-II, pro-BNP, ACTH, FC, NE, MDA, 8-iso-PG, HSP27, HSP70, PCT, CRP, CCL18 and MSP contents of ulinastatin group 7 d after treatment were significantly lower than those of normal control group while TT3 and TT4 contents were significantly higher than those of normal control group. **Conclusion:** Ulinastatin therapy can correct the disturbance of vasoactive substances, and inhibit the oxidative stress and inflammatory response in patients with acute exacerbation of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease in the elderly, which is characterized by progressive and incompletely reversible airway limitation, and can affect the pulmonary function and daily life. Infection is the most common cause of acute exacerbation of COPD, it will progress into respiratory failure and systemic inflammatory response syndrome without timely treatment, and severe cases can cause multiple organ dysfunction and increase the death rate of the disease[1,2]. During the course progression of patients with acute exacerbation of COPD, the activation of systemic inflammatory reaction can further induce the disturbance of vasoactive substances and aggravate oxidative stress. Ulinastatin is a broad-spectrum protease inhibitor, which has anti-inflammatory and anti-oxidative activity, and has protective effect on the injury of multiple tissues[3,4]. In the following study, we analyzed the effect of ulinastatin on vasoactive substances, oxidative stress and inflammatory response in patients with acute exacerbation of COPD.

2. Case information and research methods

2.1 General information of COPD patients

A total of 92 patients with acute exacerbation of COPD who were treated in Chengdu Fifth People's Hospital between August 2013 and July 2016 were selected as the research subjects, all patients had a history of COPD and were admitted to hospital due to acute exacerbation of COPD after the respiratory infections this time, and patients combined with liver and kidney failure and those who used glucocorticoid and immune preparations recently were excluded. The 92 enrolled patients were divided into two groups by

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random number table, each with 46 cases. Ulinastatin group received ulinastatin combined with conventional drug therapy, including 29 men and 17 women that were 62-75 years old; the normal control group received conventional drug therapy, including 27 men and 19 women that were 60-74 years old. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Therapy

The conventional therapy group received treatments such as continuous low-flow oxygen uptake (2 L/min) as well as anti-infection, reducing phlegm, relaxing airway, and maintaining water electrolyte balance. Ulinastatin group received ulinastatin therapy on the basis of conventional treatment, and the method was as follows: the 100 000 units of ulinastatin injection was by intravenous drip, 2 times/d.

2.3 Serum index detection

Before treatment and 7 d after treatment, 3 mL of peripheral venous blood was collected and centrifuged to get serum, enzyme-linked immunosorbent assay kit was used to determine the contents of D-D, AT-II, pro-BNP, HSP27, HSP70, PCT, CRP, CCL18 and MSP, electrochemical luminescence kit was used to detect the contents of ACTH, FC, NE, TT3 and TT4, and radioimmunoprecipitation kit was used to detect the contents of MDA and 8-iso-PG.

2.4 Statistical methods

SPSS 19.0 software was used to input data, differences in data between two groups were by t test, and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1 Vasoactive molecules

Before treatment and 7 d after treatment, analysis of serum vasoactive molecules D-D (μg/mL), AT-II and pro-BNP (pg/mL) contents between two groups of patients was as follows: serum D-D, AT-II and pro-BNP contents were not different between two groups of patients before treatment (P>0.05); 7 d after treatment, serum D-D, AT-II and pro-BNP contents of both groups of patients were significantly lower than those before treatment (P<0.05), and serum D-D, AT-II and pro-BNP contents of ulinastatin group were significantly lower than those of normal control group (P<0.05).

3.2 Stress response hormones

Before treatment and 7 d after treatment, analysis of serum stress response hormones ACTH (pmol/mL), FC (ng/mL), NE (pg/mL), TT3 (nmol/L) and TT4 (nmol/L) contents between two groups of patients was as follows: serum ACTH, FC, NE, TT3 and TT4 contents were not different between two groups of patients before treatment (P>0.05); 7 d after treatment, serum ACTH, FC and NE contents of both groups of patients were significantly lower than those before treatment while TT3 and TT4 contents were significantly higher than those before treatment (P<0.05), and serum ACTH, FC and NE contents of ulinastatin group were significantly lower than those of normal control group while TT3 and TT4 contents were significantly higher than those of normal control group (P<0.05).

3.3 Oxidative stress products

Before treatment and 7 d after treatment, analysis of serum oxidative stress products MDA (nmol/mL), 8-iso-PG (pg/mL), HSP27 (ng/mL) and HSP70 (pg/mL) contents between two groups

Table 1.
Changes in serum vasoactive molecule contents before and after treatment.

Groups	n	Time	D-D	AT-II	pro-BNP
Ulinastatin group	46	Before treatment	6.52±0.88	93.41±10.25	621.65±80.35
		After treatment	3.41±0.49[ab]	52.13±6.58[ab]	242.14±32.69[ab]
Control group	46	Before treatment	6.48±0.81	92.98±10.56	622.04±83.38
		After treatment	5.28±0.71[a]	70.46±9.92[a]	394.57±55.26[a]

Before treatment vs. after treatment within group, [a]P<0.05; ulinastatin group vs. normal control group, [b]P<0.05.

Table 2.
Changes in serum stress response hormone contents before and after treatment.

Groups	n	Time	ACTH	FC	NE	TT3	TT4
Ulinastatin group	46	Before treatment	5.39±0.77	294.5±36.2	289.1±34.1	0.89±0.11	89.3±11.4
		After treatment	2.52±0.35[ab]	215.4±26.8[ab]	204.5±26.4[ab]	1.83±0.23[ab]	125.2±15.6[ab]
Control group	46	Before treatment	5.51±0.81	296.1±33.5	288.6±32.9	0.91±0.10	88.7±10.8
		After treatment	3.62±0.52[a]	246.5±32.9[a]	251.3±31.8[a]	1.32±0.18[a]	103.4±12.5[a]

Before treatment vs. after treatment within group, [a]P<0.05; ulinastatin group vs. normal control group, [b]P<0.05.

Table 3.
Changes in serum oxidative stress product contents before and after treatment.

Groups	n	Time	MDA	8-iso-PG	HSP27	HSP70
Ulinastatin group	46	Before treatment	8.58±1.03	37.41±5.24	3.92±0.52	365.1±47.9
		After treatment	4.06±0.62[ab]	20.32±2.89[ab]	2.03±0.35[ab]	194.5±28.5[ab]
Control group	46	Before treatment	8.72±0.95	37.73±5.61	3.98±0.58	368.3±49.2
		After treatment	5.96±0.78[a]	28.39±3.57[a]	3.11±0.42[a]	275.2±33.5[a]

Before treatment vs. after treatment within group, aP<0.05; ulinastatin group vs. normal control group, [b]P<0.05.

Table 4.
Changes in serum inflammatory response mediator contents before and after treatment.

Groups	n	Time	PCT	CRP	CCL18	MSP
Ulinastatin group	46	Before treatment	6.29±0.83	32.50±4.49	22.94±3.35	7.61±0.93
		After treatment	1.44±0.18[ab]	12.19±1.42[ab]	15.03±1.83[ab]	3.95±0.52[ab]
Control group	46	Before treatment	6.35±0.79	33.21±4.29	23.03±2.93	7.55±0.88
		After treatment	3.03±0.41[a]	19.45±2.46[a]	19.21±2.24[a]	5.72±0.72[a]

Before treatment vs. after treatment within group, [a]P<0.05; ulinastatin group vs. normal control group, [b]P<0.05.

of patients was as follows: serum MDA, 8-iso-PG, HSP27 and HSP70 contents were not different between two groups of patients before treatment (P>0.05); 7 d after treatment, serum MDA, 8-iso-PG, HSP27 and HSP70 contents of both groups of patients were significantly lower than those before treatment (P<0.05), and serum MDA, 8-iso-PG, HSP27 and HSP70 contents of ulinastatin group were significantly lower than those of normal control group (P<0.05).

3.4 Inflammatory response mediators

Before treatment and 7 d after treatment, analysis of serum inflammatory response mediators PCT, CRP, CCL18 (pg/mL) and MSP (ng/mL) contents between two groups of patients was as follows: serum PCT, CRP, CCL18 and MSP contents were not different between two groups of patients before treatment (P>0.05); 7 d after treatment, serum PCT, CRP, CCL18 and MSP contents of both groups of patients were significantly lower than those before treatment (P<0.05), and serum PCT, CRP, CCL18 and MSP contents of ulinastatin group were significantly lower than those of normal control group (P<0.05).

4. Discussion

Ulinastatin is a drug with antioxidant and anti-inflammatory activity, which has been used in the treatment of acute exacerbation of COPD in recent years, and can effectively control the disease and improve the prognosis[5,6]. However, it is not yet clear at present about the effect of ulinastatin on the illness-related molecules in patients with acute exacerbation of COPD. There are the synthesis and secretion disorder of the vasoactive substances D-D, AT-II and pro-BNP in the process of acute exacerbation of COPD, and they are related to the change of cardiac function and the hypercoagulable state of the blood. The hypoxia in patients with acute exacerbation of COPD will cause hypercoagulable state and result in the increased generation of cross-linked fibrin derivatives D-D[7]; at the same time, the change of cardiac function will promote the synthesis and secretion of the BNP, and pro-BNP is the precursor of BNP, is more stable than BNP and can reflect the formation of BNP[8,9]. In addition, the change of cardiac function will activate the RAS system and increase the AT-II secretion, resulting in vasoconstriction and affecting blood flow. In the study, analysis of the changes in vasoactive molecule contents before and after treatment showed that serum D-D, AT-II and pro-BNP contents of both groups of patients significantly decreased after treatment, and serum D-D, AT-II and pro-BNP contents of ulinastatin group after treatment were significantly lower than those of normal control group. This indicates that ulinastatin can correct the vasoactive substance disturbance, and improve the cardiac function and hypercoagulable state in patients with acute exacerbation of COPD.

The acute exacerbation of COPD will make the body in a state of stress, which causes abnormal secretion of various stress hormones. Adrenal gland is the endocrine gland that plays an important role in the stress response, and the hormones secreted by adrenal cortex and medulla significantly increase in the stress state. The adrenal cortex can synthesize and secrete the FCS under the action of pituitary trophic hormone ACTH, which can affect the water-sodium metabolism and energy metabolism, and also exert the permissive action on catecholamine hormone; the adrenal medulla is able to synthesize and secrete NE when the sympathetic nerve activity increases, which can cause vasoconstriction and myocardial contractility enhancement[10,11]. The increase of FC generation in vivo will produce negative feedback to the hypothalamus and pituitary and inhibit the secretion of various pituitary trophic hormones, and the reduction of TSH secretion leads to the reduction of thyroid hormone synthesis; at the same time, hypoxia can affect the function of hypothalamic-pituitary-thyroid axis and reduce the synthesis of thyroid hormones[12]. In the study, analysis of the changes in above stress hormone contents before and after the treatment showed that serum ACTH, FC and NE contents of both groups of patients significantly decreased while TT3 and TT4 contents significantly increased after treatment, and serum ACTH, FC and NE contents of ulinastatin group were significantly lower than those of normal control group while TT3 and TT4 contents were significantly higher than those of normal control group. This indicates that ulinastatin can reduce the stress response and correct the pathological state of stress hormone secretion disorder in patients with acute exacerbation of COPD.

The activation of stress response not only causes the secretion disturbance of various hormones, but also causes the increase of oxygen free radical generation and the activation of oxidative stress

response. In the process of continuous generation of oxygen free radicals, the tissues of multiple organs in the body can be damaged and in dysfunction, and the severe cases can cause multiple organ dysfunction[13]. Oxygen free radicals have strong affinity to the lipid composition in cells, and the oxygen free radicals generated in the process of oxidative stress activation can cause lipid peroxide, which on the one hand, generates the lipid oxidation products MDA and 8-iso-PG, and on the other hand, will cause damage to cellular structure and function[14,15]. In the process of cell oxidation damage, intracellular protective molecules HSP27 and HSP70 may be increasingly expressed as compensation, which degrade misfolded proteins and stabilize mitochondrial membrane potential to protect cells[16,17]. In the study, analysis of the changes in these oxidative stress product contents before and after treatment showed that serum MDA, 8-iso-PG, HSP27 and HSP70 contents of both groups of patients significantly decreased after treatment, and serum MDA, 8-iso-PG, HSP27 and HSP70 contents of ulinastatin group were significantly lower than those of normal control group. This suggests that ulinastatin can reduce the oxidative stress response, and reduce the generation of oxygen free radicals and corresponding oxidation products in patients with acute exacerbation of COPD.

Infection is the most common cause of acute exacerbation of COPD, and the pathogen infection can activate the cascade amplification of inflammatory response and cause the massive secretion of various inflammatory reaction mediators. PCT and CRP are sensitive indicators reflecting the degree of inflammatory response, the former is the precursor form of calcitonin, has no hormonal activity, and is synthesized and secreted in large quantities under the action of bacterial infection, and the latter is a kind of acute phase protein that is synthesized and secreted by hepatocytes under the action of pro-inflammatory cytokines[18,19]. CCL18 is an endogenous chemokine, which can promote the activation and infiltration of lymphocytes after binding the membrane receptor; MSP is the regulator of macrophagess, which can promote the migration of macrophages to the inflammatory part, activate the phagocytosis of macrophages and activate the inflammatory response[20]. In the study, analysis of the changes in the inflammation mediator contents before and after treatment showed that serum PCT, CRP, CCL18 and MSP contents of both groups of patients significantly decreased after treatment, and serum PCT, CRP, CCL18 and MSP contents of ulinastatin group were significantly lower than those of normal control group. This suggests that ulinastatin can reduce the inflammatory response and reduce the production of inflammatory mediators in patients with acute exacerbation of COPD.

Ulinastatin therapy for patients with acute exacerbation of COPD can correct vasoactive substance disorder, reduce stress and correct the pathological state of stress hormone secretion disorder, and it can also inhibit the activation of oxidative stress reaction and inflammatory response.

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