Journal of Hainan Medical University

http://www.jhmuweb.net/

Effects of salbutamol combined with ulinastatin on respiratory function, inflammation and oxidative stress in COPD patients with laparoscopic surgery

Wei He[1], Qing−Hui Yuan[2], Bing Chen[3*]

[1]*Department of Anesthesiology, Mianyang Central Hospital, Sichuan Mianyang 621000, China*

[2]*Department of Pathology, Mianyang Central Hospital, Sichuan Mianyang 621000, China*

[3]*Party Discipline Office, Mianyang Central Hospital, Sichuan Mianyang 621000, China*

ARTICLE INFO

Article history:
Received 12 Jan 2016
Received in revised form 22 Jan 2016
Accepted 15 Jan 2016
Available online 28 Jan 2016

Keywords:
COPD
Salbutamol
Ulinastatin
Oxidative stress

ABSTRACT

Objective: To analyze the effects salbutamol combined with ulinastatin on respiratory function, inflammation and oxidative stress in COPD patients with laparoscopic surgery. **Methods:** A total of 76 cases of COPD patients were brought into the study. They were randomly divided into observation group (n=38) who accepted salbutamol combined with ulinastatin treatment and the control group (n=38) who accepted single salbutamol treatment. All patients' respiratory function and inflammation levels and different levels of oxidative stress were tested. **Results:** After the treatment, the observation group patients' in-surgery SpO_2 and Compl levels were higher than the control group's, while $PETCO_2$, Paw and Raw levels were lower than those of the control group. The in-surgery AAT, ESR, NPT, AAG and SAA levels of the observation group patients were significantly lower than those of the control group. After the treatment, the observation group patients' in-surgery GR, CAT, GPX1 and TXNL1 levels were higher than the control group's, while LOX-1 level was lower than that of the control group. **Conclusions:** COPD patients receiving salbutamol combined with ulinastatin treatment can significantly improve the respiratory function in surgery, and reduce systemic inflammation and oxidative stress.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is commonly seen in clinic, and there are more hidden dangers than the general patients when they receive laparoscopic surgery. The establishment of carbon dioxide pneumoperitoneum during laparoscopic surgery has obvious effect on respiration and circulation system. The presence of airway hyper-responsiveness in COPD patients leads to high rates of spasm of trachea and decreased lung compliance[1]. Salbutamol is quick β 2 receptor activator, which can effectively relieve acute attack of bronchial asthma. Ulinastatin is the widely applied broad-spectrum protease inhibitor in recent years, which inhibits reactions between tissue inflammation factors and white blood cells, and protects lung tissues from damage[2]. This study analyzed the effects of salbutamol combined with ulinastatin on respiratory function, inflammation and oxidative stress in COPD patients with laparoscopic surgery, hereby reported as follows.

2. Data and methods

2.1. General information

A total of 76 cases of COPD patients receiving laparoscopic surgery from March 2012 to December 2014 in the hospital were

*Corresponding author: Wei He, Department of Anesthesiology, Mianyang Central Hospital, Sichuan Mianyang 621000, China.
Tel: 13881187531
E-mail: yqhmianyang@163.com
Fund project: the scientific research project of Sichuan provincial health department (No: 080218).

brought into the study. All patients were divided into observation group 38 cases and control group 38 cases according to the different treatments. In the observation group, there were 20 male cases and 18 female cases, 41-72 years old and average (54.67±8.61) years old. In the control group, there were 22 male cases and 16 female cases, 43-70 years old and average (57.43±5.98) years old. Gender, age and other basic information are not significantly different between two groups (P>0.05).

2.2. Treatment methods

After entering the operating room, two groups of patients received routine ECG monitoring, connecting blood oxygen saturation instrument and establishing peripheral venous access. After anesthesia induction by propofol, cis-atracurium and fentanyl, tracheal catheter was placed and fixed. During operation, artificial pneumoperitoneum was established by filling CO_2 into the abdomen with American Sporz automatic pneumoperitoneum machine, and the tidal volume and respiratory frequency were adjusted according to intraoperative airway pressure. Patients in the control group received salbutamol treatment alone as follows: inhalation of 200 μg salbutamol aerosol 30 min before operation. The observation group received salbutamol combined with ulinastatin treatment, and salbutamol usage and dosage were the same as those of the control group, while 10^5 U/bottle ulinastatin was diluted by physiological saline to 20 mL, and after induction of anesthesia, it was slowly intravenous bolus injected in 10 min.

2.3. Observation indexes

2.3.1. Respiratory function

Patients' Blood oxygen saturation (SpO_2), end tidal carbon dioxide partial pressure ($PETCO_2$), airway pressure (Paw), airway resistance (Raw), and chest lung compliance (Compl) levels were measured in surgery after treatment.

2.3.2. Levels of inflammatory cytokines

After treatments, inflammation associated factors including α 1 antitrypsin (AAT), erythrocyte sedimentation rate (ESR) and neopterin (NPT), α 1 acid glycoprotein (AAG) and amyloid A (SAA) were tested by enzyme-linked immunosorbent adsorption assay (ELISA).

2.3.3. Oxidative stress level

Before and after the two groups of patients were treated with different treatment methods, peripheral venous blood was collected. Glutathione reductase (GR), catalase (CAT), glutathione peroxidase (Gpx1), thioredoxin protein 1 (TXNL1) and oxidation type low density lipoprotein receptor 1 (LOX-1) levels were tested by radioimmune precipitation assay.

2.4. Statistical methods

The data in this paper was analyzed by software SPSS 23.0. T-test was applied to the two-two comparison of measurement data. P<0.05 was set to be the standard of statistical significance.

3. Results

3.1. Respiratory function

COPD Patients have reduced based lung function. The laparoscopic pneumoperitoneum will cause further respiratory function injury, and severe cases may even cause postoperative respiratory failure. Real-time monitoring of the respiratory function during operation process is necessary index to judge therapeutic effect and prognosis. Two groups of patients' SpO_2, Compl, $PetCO_2$, Paw and Raw levels in operation were monitored in the study. The results showed that after the patients in the observation group received salbutamol combined with ulinastatin treatment, SpO_2 and Compl levels were higher than those of the control group during operation while $PetCO_2$, Paw and Raw levels were lower (P<0.05), shown in Table 1.

3.2. Levels of inflammatory cytokines

COPD patients are accompanied with obvious local and systemic inflammation. Surgical trauma will aggravate the inflammatory reaction and even lead to disease aggravation. The effective control of systemic inflammatory state is important means to ensure successful operation and smooth recovery. So intraoperative serum levels of inflammatory factors were detected in the study and the following results were obtained: after patients in the observation group received salbutamol combined with ulinastatin treatment, the intraoperative AAT, ESR, NPT, AAG and SAA levels were lower than those of the control group (P<0.05) , shown in Table 2.

3.3. Oxidative stress level

Both COPD disease itself and surgical trauma can make the patient in a state of oxidative stress. Severe oxidative stress increases the body consumption and inhibits physical rehabilitation. The determination of levels of oxidative stress indicators is an effective way to reflect treatment effect and predict treatment outcome. Serum oxidative stress and anti-oxidative stress indexes were detected in the study, and results showed as follows: GR, CAT, Gpx1 and TXNL1 levels in the observation group patients after the treatment were higher than those in control group while LOX-1 level was lower than that of the control group (P<0.05), as shown in Table 3.

Table 1

Comparison of respiratory function indexes between groups.

Groups	SpO_2 (%)	$PETCO_2$ (mmHg)	Paw (cmH_2O)	Raw (cmH_2O·S/L)	Compl (mL/cmH_2O)
Observation	99.13±0.37	35.82±3.11	25.18±3.76	19.37±1.61	50.66±6.81
Control	96.78±0.72	42.63±4.07	34.02±3.59	24.56±2.33	36.27±5.98
t	5.294	7.183	8.663	6.835	8.274
P	<0.05	<0.05	<0.05	<0.05	<0.05

Table 2

Comparison of the levels of inflammatory cytokines between the groups.

Groups	AAT (mg/dL)	ESR (mg/dL)	NPT (nmol/L)(mg/dL)	AAG (mg/dL)	SAA (ng/L)
Observation	142.37±12.76	17.23±1.54	8.32±0.76	132.83±11.05	734.28±69.95
Control	185.62±17.93	39.81±3.77	21.85±1.77	289.61±20.76	1 327.55±176.39
t	8.342	7.093	9.172	12.374	11.183
P	<0.05	<0.05	<0.05	<0.05	<0.05

Table 3

Comparison of oxidative stress levels between groups.

Groups	GR (U/mL)	CAT (μg/mL)	GPX1 (mg/L)	TXNL1 (μg/mL)	LOX-1 (μg/mL)
Observation	19.27±1.63	1.24±0.14	1.98±0.15	27.48±2.33	2.18±0.19
Control	11.58±0.98	0.53±0.05	1.01±0.13	5.69±0.48	11.27±1.45
t	7.384	6.273	5.998	9.734	8.374
P	<0.05	<0.05	<0.05	<0.05	<0.05

4. Discussions

COPD is chronic respiratory disease that is characterized by restricted flow, whose main performances are sustained chronic cough sputum, dyspnea, wheezing and chest tightness, and severe cases may even involve the circulatory system and nervous system. Our epidemiological survey of the prevalence rate of COPD among people over 40 years of age is 8.2%[3]. Laparoscopic surgery can lead to changes in the patients' respiratory and circulatory function. When COPD patients undergo laparoscopic surgery, pneumoperitoneum is established, intra-abdominal pressure rises, the thoracic expansion is limited and lung compliance decreases, and thus the operative risk coefficient is higher. The higher the carbon dioxide pressure in laparoscopic surgery, the fuller the abdominal wall and abdominal viscera's separation, and it is convenient for operation and reduces the chance of accidental injury. Therefore, in the clinical treatment of adverse reactions of patients with COPD, it is more likely to use other treatment rather than reducing the abdominal pressure[4,5].

Salbutamol is β 2 receptor activator, which can effectively activate β 2 adrenergic receptor. The activated receptor binding with G protein and coupling with adenosine activating enzyme can increase the intracellular cAMP levels, activate protein activation system, effectively relax airway smooth muscle and reduce airway resistance[6]. It only takes salbutamol 15-30 min to reach the peak concentration after inhalation. It mainly acts on small airway and has definite bronchial dilatation effect. Ulinastatin is a kind of protease inhibitors secreted by the liver and a kind of human endogenous anti-inflammatory substances, which binds with trypsin and other enzymes after metabolism in urine to play inhibition activity, promote the degradation of enzymes, maintain the lysosomal membrane stability, clear oxygen free radicals and improve lung ischemia reperfusion oxygen injecting synthetic index and pulmonary compliance[7,8]. This study applied salbutamol combined ulinastatin treatment to the COPD patients with laparoscopic surgery. Detection of respiratory function found: observation group patients' SpO_2, Compl levels were higher than the control group' while $PetCO_2$, Paw and Raw levels were lower than control group' (P<0.05). Small airway pathological changes were the pathological basis of ventilation disorder of COPD patients. While laparoscopic pneumoperitoneum is established, the changes of COPD patients' respiratory mechanics are more obvious. Combined application of salbutamol and ulinastatin helps the expansion of the small airway as well as reduces airway injury and optimizes lung compliance, and eventually leading to great improvement of respiratory parameters.

Long-term airway inflammation is the underlying disease of COPD patients. Anesthesia intubation and ventilation stimulation can induce trachea spasm, manifested as increasing airway pressure and injury of trachea bronchus, which can stimulate systemic release of inflammatory mediators and cause lung damage. And that is the main reason of patients' incompetence pulmonary function[9]. Salbutamol's effect of expanding airway smooth muscle is generated quickly, which can increase cilia clearance function, reduce vascular permeability and inhibit the inflammatory edema. Ulinastatin also helps to inhibit the production of endogenous inflammatory substances. Combined application of the two drugs in laparoscopic surgery can effectively reduce the systemic inflammatory response, and may become an important basis for improving the respiratory function of patients. 1 antitrypsin (AAT) is an acute phase protein, whose level rises in the body during the invasion of pathogenic microorganisms and tissue injury and other inflammatory stimuli processes. Studies have confirmed that the AAT levels are correlated with the degree of inflammation, and with the patient's recovery, it returns to normal level in a relatively short time. So AAT is a good indicator to monitor the course of the disease and to predict treatment outcomes[10]. ESR, on behalf of the rate of erythrocyte sedimentation, is common detection index in clinical. ESR speed is related to the blood viscosity and erythrocyte aggregation force, which can reflect the inflammation and other systemic diseases. When the inflammatory diseases occur, ESR can be significantly accelerated. Neopterin (NPT) is the low molecular pteridine compounds in the body fluids, which is produced by activated macrophage and secreted to the extracellular intracellular in protease form. It acts on gelatin and collagen, and is considered to be associated with inflammation. Studies have confirmed that the level of NPT in patients with active inflammation is rising, and gradually declines when the condition is improved, suggesting that NPT is an effective and objective indicator to judge the patient's inflammatory

condition. 1 acid glycoprotein (AAG) is synthesized in liver and white blood cell, and also belongs to acute phase proteins. The rising trend of AAG at the early stage of acute inflammation is consistent with C-reactive protein and has better increase trends. The good sensitivity makes it currently one of the effective indexes for detection of the degree of inflammatory reaction[11,12]. Amyloid A (SAA) is a precursor of amyloid A protein. The latest researches show that SAA can promote the entry of neutrophils and monocytes into inflammatory lesions and induce inflammation and immune response. SAA is considered to be one of the pro-inflammatory factors, which is produced in the early stage of the inflammatory reaction, and it also reflects the degree of the inflammatory reaction.

COPD patients airway were in states of hypersensitivity and the establishment of pneumoperitoneum in laparoscopic surgery and surgical stimulation both have harmful effects on the patients. In severe cases, patients' systemic consumption state is worse and acute stress reaction is generated. Severe oxidative stress reaction can aggravate COPD condition, deteriorate of lung function in surgery, and have a great blow to patients' postoperative recovery[13]. Glutathione reductase (GR) is an enzyme that turns oxidized glutathione catalytic into deoxidation type by using deoxidate NAD. Studies suggest that GR is the key regulatory enzyme of NO signaling pathway. And NO plays a role inflammatory reaction. Therefore, GR also plays an important role in regulating the inflammatory response. When the level of GR decreases, the resistance to oxygen free radicals decreases, the oxidation substances increase in body and the effect of NO is strengthened, and the level of oxidative stress increases. Excessive reactive oxygen species can make the unsaturated fatty acids generate peroxide lipid, resulting in damage to the biological membrane. Excessive levels of oxidative stress can cause changes of a variety of protein levels, destruct nucleic acids and chromosomal status, and cause huge damage to the whole body tissue cells. The key step of anti-oxidative stress is to inhibit the level of peroxide in vivo. Catalase (CAT), glutathione peroxidase (Gpx1), oxygen and thioredoxin protein 1 (TXNL1) belong to antioxidant system factors. Studies have shown that the factor levels and oxidative stress are inversely proportional, and the real-time monitoring of them helps to understand the patients' stress state and predict the final treatment outcome[14,15]. Oxidized low density lipoprotein receptor 1 (LOX-1) is an oxidative factor, which can induce the expression of LOX-1. LOX-1 is a marker of oxidative damage, and is a specific ligand of oxLDL. A large number of clinical studies have indicated that oxidative damage promotes smooth muscle cells, monocytes and macrophages apoptosis and phagocytosis through the expression of LOX-1. So LOX-1 is directly involved in the oxidative stress reaction process. The research results showed that: after the treatment, the observation group patients' in-surgery GR, CAT, GPX1 and TXNL1 levels were higher than the control group' while LOX-1 level was lower than the control group' (P<0.05), suggesting that COPD patients receiving salbutamol combined with ulinastatin treatment could significantly reduce systemic oxidative stress, help the realization of a success laparoscopic surgery and protect patients from postoperative severe stress reaction damage.

To sum up, we can draw the following conclusions: salbutamol combined with ulinastatin treatment can effectively enhance the respiratory function of COPD patients receiving laparoscopic surgery, and reduce systemic inflammation and oxidative stress level, which is worth clinical promotion.

References

[1] Sharafkhaneh A, Altan AE, Colice GL. A simple rule to identify patients with chronic obstructive pulmonary disease who may need treatment reevaluation. *Respir Med* 2014; **108**(9): 1310-1320.

[2] Kirby M, Pike D, Coxson HO. Hyperpolarized (3) He ventilation defects used to predict pulmonary exacerbations in mild to moderate chronic obstructive pulmonary disease. *Radiology* 2014; **273**(3): 887-896.

[3] Bateman ED, Mahler DA, Vogelmeier CF. Recent advances in COPD disease management with fixed-dose long-acting combination therapies. *Expert Rev Respir Med* 2014; **8**(3): 357-379.

[4] Genc A, Ucok K, Sener U. Association analyses of oxidative stress, aerobic capacity, daily physical activity, and body composition parameters in patients with mild to moderate COPD. *Turk J Med Sci* 2014; **44**(6): 972-979.

[5] Erden ES, Motor S, Ustun I. Investigation of Bisphenol A as an endocrine disruptor, total thiol, malondialdehyde, and C-reactive protein levels in chronic obstructive pulmonary disease. *Eur Rev Med Pharmacol Sci* 2014; **18**(22): 3477-3483.

[6] Shergis JL, Di YM, Zhang AL. Therapeutic potential of Panax ginseng and ginsenosides in the treatment of chronic obstructive pulmonary disease. *Complement Ther Med* 2014; **22**(5): 944-953.

[7] Mordukhovich I, Lepeule J, Coull BA. The effect of oxidative stress polymorphisms on the association between long-term black carbon exposure and lung function among elderly men. *Thorax* 2015; **70**(2): 133-137.

[8] Yin L, Lensmar C, Ingelsson E, Back M. Differential association of chronic obstructive pulmonary disease with myocardial infarction and ischemic stroke in a nation-wide cohort. *Int J Cardiol* 2014; **173**(3): 601-603.

[9] Akpinar EE, Hosgun D, Akpinar S, Atac GK, Doganay B, Gulhan M. Incidence of pulmonary embolism during COPD exacerbation. *J Bras Pneumol* 2014; **40**(1): 38-45.

[10]Wang Y, Shumansky K, Sin DD, Man SP, Akhabir L, Connett JE, et al. Associations of interleukin-1 gene cluster polymorphisms with C-reactive protein concentration and lung function decline in smoking-induced chronic obstructive pulmonary disease. *Int J Clin Exp Pathol* 2015; **8**(10): 13125-13135.

[11]Mascalchi M. Pulmonary function tests and computed tomography lung attenuation in chronic obstructive pulmonary disease. *J Thorac Dis* 2015; **7**(11): 1882-1884.

[12]Ostrowski S, Marcinkiewicz A, Kosmider A, Walczak A, Zwolinski R, Jaszewski R. Artificial aortic valve dysfunction due to pannus and thrombus - different methods of cardiac surgical management. *Kardiochir Torakochirurgia Pol* 2015; **12**(3): 199-203.

[13]Chan TC, Wang HW, Tseng TJ, Chiang PH. Spatial clustering and local risk factors of chronic obstructive pulmonary disease (COPD). *Int J Environ Res Public Health* 2015; **12**(12): 15716-15727.

[14]Polikutina OM, Slepynina YS, Bazdyrev ED, Karetnikova VL, Barbarash OL. Rate of detection of atherosclerosis in patients with ST elevation myocardial infarction and concomitant chronic obstructive pulmonary disease of light or moderate degree of severity. *Kardiologiia* 2015; **55**(7): 26-31.

[15]Ehteshami-Afshar S, FitzGerald JM, Doyle-Waters MM, Sadatsafavi M. The global economic burden of asthma and chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2016; **20**(1): 11-23.