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Original Research Article

Effects of aerosolized inhalation of N-acetylcysteine combined with high flow nasal cannulae oxygen therapy on inflammation, oxidative stress, and cognitive function in patients with severe pulmonary infection complicated with respiratory failure

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Abstract

Purpose: *To investigate the effects of aerosolized inhalation of N-acetylcysteine (NAC) combined with high-flow nasal cannulae oxygen therapy on serum inflammation, oxidative stress, and cognitive function in patients with severe pulmonary infection complicated with respiratory failure.*
Methods: *A total of 50 patients diagnosed with severe pulmonary infection complicated with respiratory failure were randomly divided into the study and control groups, respectively. Serum oxidative stress, inflammation, and cognitive function were determined after treatment intervention. The effect of aerosol inhalation of NAC combined with high flow-nasal cannulae oxygen therapy was assessed.*
Results: *General clinical data such as age, lung function, etc, did not show any difference between the study and control groups ($p > 0.05$). Dyspnea was scored in the Study group after treatment. Serum malondialdehyde (MDA), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) decreased ($p < 0.05$), while cognitive scores and serum total antioxidant capacity of the Study group increased ($p < 0.05$); There was no significant difference in serum superoxide dismutase levels between the two groups ($p > 0.05$).*
Conclusion: *Aerosolized inhalation of NAC combined with high-flow nasal cannulae oxygen therapy has anti-inflammatory and antioxidant effects, which can improve cognitive dysfunction in patients with severe pulmonary infection complicated with respiratory failure, and may provide a new clinical treatment strategy for severe pulmonary infection complicated with respiratory failure.*

Keywords: *N-acetylcysteine, High-flow nasal cannulae oxygen therapy, Respiratory failure, Oxidative stress*

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INTRODUCTION

With the improvement of clinical treatment, most patients with severe pulmonary infection have been effectively treated, but the effect of routine treatments such as antibiotics in patients with severe infection complicated with respiratory failure will become worse. Therefore, there is an

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urgent need to find new treatments to improve outcomes. Untreated patients with respiratory failure can lead to multiple organ failures, and oxygen therapy is the basic treatment measure to relieve dyspnea [1]. High-flow nasal cannula oxygen therapy (HFNC) delivers a concentration of oxygen and high-flow gas through a nasal catheter. HFNC can make the input gas reach the most suitable temperature and humidity for the human body. When the patient is in respiratory failure, conventional oxygen therapy may not be sufficient to support breathing, whereas HFNC provides airflow of up to 60 L/min, which is sufficient to meet oxygen demand [2]. Previous studies have shown that HFNC quickly relieves dyspnea symptoms [3] and improves oxygenation in a variety of ways, such as reducing the number of non-effective nasopharynx cavities PEEP can increase end-expiratory lung volume. While NAC exerts positive effects such as antioxidant, anti-inflammatory and prevention of cognitive impairment [4], different dose intensities and protocol designs are applied in different studies. The positive results are difficult to replicate, and there is no consensus yet. Therefore, more clinical studies are required to further determine the efficacy and standardize the treatment. This study aimed to investigate the effects of aerosolized inhalation of NAC combined with HFNC on oxidative stress, inflammation, and cognitive function in patients with severe pulmonary infection complicated with respiratory failure.

METHODS

General patient information

A total of 50 patients with severe pulmonary infection complicated with respiratory failure in the Department of Respiratory Medicine, the Second Affiliated Hospital of Hainan Medical University from March 2018 to March 2019 were randomly selected. The study was approved by the ethics committee of The Second Affiliated Hospital of Hainan Medical University (approval no. 2016NS61981C), and complied with the guidelines of the Declaration of Helsinki [5].

Severe pulmonary infection was diagnosed based on the guidelines developed by the IDSA/ATS. Diagnostic criteria for respiratory failure: PaO2/FiO2 < 285.7 mmHg in patients at sea level and resting status. Patients were randomly divided into the study group (12 males and 13 females) with a mean age of (56.36 ± 9.95) years (range, 40 - 73 years) and control group (14 males and 11 females), with a mean age of (57.72 ± 9.81) years (range, 45 - 78 years). There was no significant difference in general clinical data between the two groups ($p > 0.05$).

Treatments

Patients in the Study group were treated with aerosolized inhalation of NAC solution (Zanbon Group, Italy; drug approval no.: H20110405; specification: 3 mL:0.3 g) and HFNC, while control group was given conventional drugs and continuous positive nasal pressure ventilation. The dose of NAC solution was set at 1.5 mL and added with 0.9 % sodium chloride to reach 2 mL. Aerosolized inhalation was performed for 5 min, twice a day for 10 days. No allergy, drug fever, and other adverse reactions occurred during the treatment. Fisher-Paykel high-flow oxygen-absorbing instrument and nasal catheter were used to provide oxygen at 35 L/min suction flow, and the SpO_2 was adjusted to reach > 94 % during the first 5 min for 60 min. Treatment with transnasal continuous positive pressure ventilation: patients were maintained on 94% SpO_2 for more than 60 min using an infant blood flow system ventilator at a dose flow rate of 3 - 10 L/min.

Baseline data

Age, sex, medical history records, routine physical examination data, and Pneumonia Severity Index (PSI) scores were recorded. Physiological parameters such as respiratory rate, heart rate, mean arterial pressure, SpO_2, and degree of dyspnea were recorded to assess cognitive function.

Pneumonia severity assessment

PSI score was used to assess the severity of pulmonary infection: grade I did not require a score, grade II ≤ 70, grade III 71 - 90, and grade IV - V 90. Dyspnea was assessed on a scale of 0 to 10. The higher the value, the more severe the dyspnea.

Assessment of cognitive function

The simple intelligent mental state detection volume (MMSE) and the Montreal cognitive assessment scale (MoCA) scored cognitive function. Physiological variables were recorded at 5, 15, 30, 60, and 75 min before and after the onset of each oxygen therapy.

Determination of various serum indices

On day 10 after the combination therapy, the venous blood of the patients was collected to

detect serum oxidative stress and inflammatory response. After centrifuging for 10 min (4 ℃, 2000 g), the serum was collected, and the levels of MDA, SOD, and TAOC in serum were measured by ELISA kits of MDA, SOD, and TAOC, respectively (Jiancheng Biological Co., Nanjing, China). Inflammatory markers TNF-α and IL-6 in serum were measured by ELISA kits (Biological Co., Shanghai, China). MDA was used to measure the degree of oxidative damage, and SOD and TAOC were used to measure the antioxidant capacity.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (X ± S), and two independent samples were used for the non-parametric test. Count data (%) were compared by χ^2. $P < 0.05$ was considered statistically significant.

RESULTS

General clinical profile of patients

Among the 50 patients in the two groups, no statistical differences existed with regard to age, gender ratio, and PSI grade *(p* > 0.05) (Table 1).

Physiological variables

Before treatment, the score of dyspnea degree, respiratory rate, heart rate, mean arterial pressure, blood oxygen saturation SpO_2, and other physiological indexes of the two groups were recorded, which presented no statistical difference (*p* > 0.05). The study group was given oxygen therapy and HFNC to improve respiration, and the control group was given continuous positive pressure ventilation. The dyspnea scores of the two groups decreased after 5 min and 15 min of oxygen therapy but indicated no statistical difference *(p* > 0.05). However, after 30, 60 and 75 min of oxygen therapy, the dyspnea scores of the study group decreased versus the control group (*p* < 0.01). Except for respiratory rate and SpO_2 (*p* > 0.05), heart rate decreased *(p* < 0.001), while mean arterial pressure increased (*p* < 0.01) in the study group (Table 2).

Table 1: General clinical data

Variable	Study group (n =25)	Control group (n =25)	*P*-value
Gender ratio (male/female)	12/13	14/11	0.778
Age	56.36±9.95	57.72±9.81	0.698
PSI			
PSI-I	3(12%)	4(16%)	0.779
PSI-II	15(60%)	12(48%)	
PSI-III	7(28%)	9(36%)	

Oxidative stress indices

To eliminate the effect of basal values, serum oxidative stress and inflammatory markers were not significant before inhalation of NAC *(p* > 0.05). On day 10 after treatment, repeated measurements of oxidative stress indices revealed that serum MDA levels decreased *(p* <0.05) and SOD and TAOC levels increased *(p* <0.05) in groups; The changes in serum MDA and TAOC in the study group were greater *(p* < 0.01), but serum SOD did not *(p* > 0.05) (Table 3).

Table 2: Physiological variables

Parameter	Pre-treatment			After treatment		
	Study group	*Control group*	*P-value*	*Study group*	*Control group*	*P*-value
Dyspnea score	6.40±1.15	6.52±1.12	0.703	2.16±1.07	3.52±1.12	0.000
Respiratory frequency	32.36±3.13	31.60±3.06	0.234	25.88±2.15	26.12±1.45	0.945
Heart rate	109.68±3.34	109.08±3.36	0.762	96.36±3.09	102.20±1.85	0.000
Mean arterial pressure	100.12±4.58	99.56±3.65	0.413	93.88±1.76	92.60±2.47	0.002
SPO_2	85.16±3.88	86.84±1.91	0.060	95.48±1.08	95.24±2.07	0.778

Table 3: Oxidative stress indices

Parameter	Pre-treatment			After treatment		
	Study group	*Control group*	*P-value*	*Study group*	*Control group*	*P-value*
MDA (nmol/ml)	7.22±1.05	7.01±1.19	0.503	5.05±1.01	6.08±1.17	0.005
SOD (U/ml)	59.64±11.50	62.80±13.30	0.377	68.52±12.45	69.08±13.52	0.734
TAOC(U/ml)	5.15±2.25	5.54±1.69	0.546	9.53±2.59	7.29±1.71	0.002

Table 4: Inflammatory indexes

Parameter	Pre-treatment			After treatment		
	Study group	***Control group***	***P*-value**	***Study group***	***Control group***	***P*-value**
TNF-α(pg/ml)	23.56±3.45	22.12±3.17	0.141	10.40±2.66	15.16±3.04	0.000
IL-6(pg/ml)	10.72±3.72	11.64±3.93	0.190	6.16±1.31	9.08±2.53	0.000

Table 5: Cognitive function

Parameter	Pre-treatment			After treatment		
	Study group	***Control group***	***P-value***	***Study group***	***Control group***	***P-value***
MMSE	23.12±2.13	22.76±1.81	0.563	27.16±0.99	24.44±2.00	0.000
MoCA	23.72±1.21	23.04±1.69	0.055	27.40±0.96	25.24±1.27	0.000

Inflammatory indices

On day 10 after inhalation of NAC, TNF-α and IL-6 levels reduced *(p* < 0.05) in groups, particularly in the study group *(p* < 0.001; Table 4).

Cognitive function

As Table 5 shows, the patients in both groups had mild cognitive impairment before treatment. The cognitive test scores increased after treatment (*p* <0.05), but MMSE and MoCA scores were more obviously elevated in the study group (*p* < 0.001).

DISCUSSION

Severe pulmonary infection is a progressive infection that can develop from local pulmonary infection to systemic infection complicated with respiratory failure, septic shock, and so on. Roles of oxidative stress and inflammatory response have been clarified in severe pulmonary infection.

When pathogenic microorganisms invade the human body, they can directly cause damage to the lungs, and the body rapidly releases a glut of inflammatory factors, which in turn stimulate the release of reactive oxygen species (ROS). Neutrophils and macrophages used ROS and lysosomal enzymes to eliminate invasive ROS of microbial; overproduction of ROS, in turn, puts the body in an oxidative/antioxidant imbalance, leading to lipid peroxidation in cell membranes, inactivation of protein denaturation, and destruction of nucleic acids [6]. Compared with healthy volunteers, patients with severe community-acquired pneumonia had more severe oxidative damage [7]. After respiratory syncytial virus infection, the antioxidant system of patients is inhibited, leading to oxidative damage in lung tissue [8].

NAC, as the precursor of synthetic GSH, interacts with ROS electrophilic groups and improves the antioxidant capacity. NAC attenuates cigarette smoke-induced alveolar type II cell damage by eliminating ROS activity *in vitro* [9]. Oral NAC (600 mg/d) improves symptoms, delays disease progression, and reduces MDA concentrations in chronic obstructive pulmonary disease patients [10]. Previous studies mostly used oral NAC administration, but in this study, aerosol inhalation of NAC solution was chosen to make NAC directly reach the lesion site, with quick effect and high bioavailability. *In vitro* aerosolized inhalation of NAC can reduce inflammatory response during experimental porcine lung transplantation [11]. Aerosol inhalation of NAC in patients with idiopathic pulmonary fibrosis relieves disease progression [12].

This study also found that serum MDA decreased and SOD and TAOC increased after treatment, and the change in MDA and TAOC levels was more obvious in the Study group, which was similar to the previous study showing that serum SOD activity did not change after NAC treatment in rats with lung injury [13]. Among mammals, there are three SOD subtypes. NAC only increased Mn-SOD expression but not other antioxidant enzymes in hyperoxic lung injury models with overexpression of manganese [14]. No changes in serum SOD levels were found between the two groups, which may be related to the different types of SOD detected.

Also, the paper discovered that the serum levels of TNF-α and IL-6 were higher before treatment, indicating that the inflammatory reaction after infection was more intense. Lipopolysaccharide (LPS), a pathogenic component of pathogenic microorganisms, was used to induce macrophages to establish CAP models. The TNF-α and IL-6 transcription levels in macrophages were up-regulated and the cells

secreted large amounts of TNF-α and IL-6 [15]. When pathogenic microorganisms enter the lung tissue, LPS activates TOLL-like receptors on the surface of monocytes, and activates nuclear factor KB (NF-kB), promoting the secretion of TNF-α and IL-6. Proinflammatory factors recruit inflammatory cells and further promote the inflammatory response, leading to the progression from mild to severe lung infection. Therefore, serum TNF-α and IL-6 in patients with severe lung infection are higher than those in the normal population or patients with mild infection.

NAC exerts anti-inflammatory effects in the body. A549 cells transfected with influenza virus (strains A and B) and RSV could inhibit the nuclear translocation and phosphorylation of NF-κB, thereby inhibiting the expression and release of TNF-α and IL-6 [16]. NAC inhibited TNF-α-induced activation of NF-kB in alveolar macrophages through different mechanisms [17], and inhibited cytokine (TNF-α/IL-1β)-induced adhesion molecule expression and IL-8 release in endothelial cells and bronchial epithelial cells in a concentration-dependent manner [18]. In this study, serum TNF-α and IL-6 decreased after treatment. especially after aerosolized inhalation of NAC. These results suggest that NAC protects the lung tissue from inflammatory damage by reducing the expression of TNF-α and IL-6.

Severe pulmonary infection complicated with respiratory failure, in addition to causing damage to the patient's lungs and dyspnea, also damages the nerve center, thereby affecting the cognitive function of patients. HFNC treatment can improve the symptoms of dyspnea, and restore respiratory rate, heart rate, and other physiological indicators after tracheal extubation, and the clinical effect is better than conventional oxygen therapy [19].

In this study, aerosolized inhalation of NAC combined with HFNC can regulate the heart rate and respiratory rate, and improve dyspnea symptoms. Improvement in cognitive function in patients in the study group may be associated with HFNC comfort, and NAC is the precursor within GSH brain. Besides, the application of NAC also inhibits the dysregulation of glutamate, a key neurotransmitter in the brain, and abnormal activation of inflammatory cells, thereby reducing the negative cognitive regulation of inflammation. Continuous hypobaric oxygen therapy can improve patients' confidence in treatment, reduce negative emotions, and contribute to disease recovery and cognitive function improvement. Respiratory rate and SpO_2 show no significant difference between groups, which may be related to HFNC being an open oxygen supply system. The level of PEEP provided by HFNC is around 7 cm H20 and is also affected by mouth opening breathing, gender, and other factors.

CONCLUSION

Aerosolized inhalation combined with HFNC has anti-inflammatory and antioxidant effects, and can attenuate cognitive impairment in patients with severe pulmonary infection complicated with respiratory failure. This study may provide a new clinical treatment strategy for severe pulmonary infection complicated with respiratory failure.

DECLARATIONS

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Ethical approval

This study was approved by the ethics committee of The Second Affiliated Hospital of Hainan Medical University (approval no. 2016NS61981C).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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