ORIGINAL RESEARCH

Efficacy and Safety Analysis of Piperacillin Tazobactam in Combination With High Frequency Chest Wall Oscillation in Patients With COPD Coupled With Pneumonia

Li Li, BSN; Qiong Feng, BSN; Qinghua Meng, MM; Fajiu Li, MM

ABSTRACT

Context • Chronic obstructive pulmonary disease (COPD) is a common, chronic inflammatory disease of the airway, and acute exacerbation of COPD (AE-COPD) refers to the manifestations of inflammation in the lungs that appear within a short period of time. Some patients contract pneumonia, and they can be prone to recurrent attacks of AE-COPD combined with pneumonia. The efficacy of conventional treatments isn't generally satisfactory.

Objective • The study intended to investigate the effectiveness and safety of piperacillin tazobactam in combination with the use of high-frequency chest-wall oscillation (HFCWO) to produce expectoration for the treatment of pneumonia in patients with AE-COPD and to provide a reference for clinical treatment.

Design • The research team designed a prospective, randomized controlled trial.

Setting • The study took place at the Sixth Hospital of Wuhan of the Affiliated Hospital of Jianghan University in Wuhan, China.

Participants • Participants were 92 patients who had been admitted to the hospital between January 2020 and November 2021 with AE-COPD combined with pneumonia.

Intervention • Using the random number table method, the research team randomly assigned participants to one of two groups, an intervention group or a control group, each with 46 participants. The control group received conventional treatment with oxygen, antibiotics, antispasmodics, antiasthmatic drugs, and phlegmolytic drugs as well as HFCWO for sputum removal. In addition to those treatments, the intervention group received piperacillin tazobactam.

Outcome measures • The research team measured the treatment's efficacy at one day postintervention. At baseline and at one day postintervention, the study also measured pulmonary function, laboratory indexes, and blood-gas-analysis indexes. In addition, the research team identified the time of disappearance of clinical symptoms, including the disappearance of cough, sputum, dyspnea, and pulmonary rales; calculated the length of hospital stay, and evaluated the treatment's safety.

Results • Postintervention, the intervention group's clinical efficacy was significantly higher than that of the control group ($P < .05$), and the group's cough, coughing of sputum, dyspnea, disappearance time of pulmonary rales, and hospitalization times were all significantly lower than those in the control group ($P < .05$). The FEV1, FVC, FEV1% and FEV1/FVC levels were higher in both groups postintervention than at baseline and were significantly higher in the intervention group than in the control group ($P < .05$). Postintervention, the levels of IL-2, IL-10, TNF-α, CRP and PCT were lower in both groups than at baseline, and the intervention group's levels were significantly lower than those in the control group ($P < .05$). Postintervention, the PaCO2 level decreased and PaO2 and SaO2 levels increased in both groups compared to baseline; the intervention group's PaCO2 level was lower and PaO2 and SaO2 levels were higher than those in the control group. During the treatment, no adverse reactions occurred in the control group, and one participant had a decreased appetite in the intervention group; the incidence of adverse reactions in that group was 2.17% (1/46). That participant received no special treatment, and the condition improved after stopping the drug.

Conclusion • Piperacillin tazobactam combined with HFCWO for sputum evacuation can effectively treat patients with pneumonia in acute exacerbation of COPD, with high safety. The treatment is worthy of clinical application. (*Altern Ther Health Med.* 2023;29(1):124-129).

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Chronic obstructive pulmonary disease (COPD) is a common, chronic inflammatory disease of the airway in clinics, with an incomplete, reversible airflow limitation and progressive exacerbation as the main manifestations. Several studies have pointed out that COPD has become the third cause of death worldwide.[1,2] The mortality rate with COPD has become an important health problem in China due to the large smoking population, and the prevalence of COPD in people over 40 years old is about 8.3%.[1,2]

Acute exacerbation of COPD (AE-COPD) refers to the manifestations of inflammation in the lungs that appear in COPD patients within a short period of time, such as coughing, increased sputum and wheezing symptoms, and purulent or mucus sputum.[3-5] Some patients contract pneumonia, and they can be prone to recurrent attacks of AE-COPD combined with pneumonia that can cause acute respiratory failure and even lead to death, making the disease a serious threat to patients' lives.[3-5]

COPD produces inflammatory mediators in the lungs that can enter the bloodstream and promote systemic inflammation, especially in patients with AE-COPD combined with pneumonia.[6,7] Cytokines are small-molecule proteins that nucleated cells secrete for signaling and are of great value in respiratory diseases, especially in chronic inflammation, where their release can grow through self-regulation and mutual regulation to target inflammatory factors.[8]

Interleukins play an important role in the transmission of information, activation of inflammatory cells, and regulation of inflammatory responses. The relationship between inflammatory-factor imbalance and AE-COPD combined with pneumonia is well established, and T helper 2 (Th2) cells secrete cytokines such as interleukin 10 (IL-10) that are essential for maintaining homeostasis in the body.[9,10] Th1 cells secrete cytokines such as IL-2 that can contribute to Th1 expansion, and have an important role in anti-infection therapies; reduced IL-2 levels can lead to a decrease in the body's immune viability, which can have an impact on COPD patients' immune function.[11]

Tumor necrosis factor alpha (TNF-α) is the initiator of the inflammatory response; activated monocytes and macrophages mainly secrete it; and they can be involved in the remodeling and obstruction process in the COPD airway through the airway's chronic inflammatory network.[12] C-reactive protein (CRP) is an important inflammatory factor, and increased levels indicate a more severe inflammatory response.[13] Procalcitonin (PCT) is an inflammatory mediator and an important marker of inflammatory factors.[14]

Patients with AE-COPD combined with pneumonia should receive treatment in a timely manner to preserve respiratory flow and provide oxygen in combination with conventional treatments, such as anticough, antiasthmatic, and anti-infective therapies.[15] However, due to the long treatment time, the efficacy of conventional treatments alone isn't generally satisfactory.

Producing expectoration using high-frequency chest-wall oscillation (HFCWO) is an emerging modality in chest physiotherapy, and the device belongs to a group of devices for oscillatory airway clearance, which are mainly used to expel airway secretions.[5,16] By putting an inflatable jacket undershirt on a patient, this technique for sputum evacuation can reduce the impact that human manipulation produces and can take over that manipulation as it gradually decreases when those interventions by medical personnel decrease.

The treatment can produce simultaneous oscillations from multiple sites and effectively expel secretions produced by alveoli, deep small bronchi, main bronchi, and trachea, facilitating sputum expulsion.[17] Nicolini et al's study pointed out that the use of HFCWO to produce expectoration can effectively induce sputum expulsion in patients with AE-COPD combined with pneumonia, with remarkable results [18]

Piperacillin tazobactam is a broad-spectrum antibacterial drug synthesized from piperacillin and tazobactam. It belongs to the category of broad-spectrum, β-lactamase inhibitors and semisynthetic penicillin, and clinical studies have shown it to be effective in the treatment of community-acquired pneumonia, bronchiectasis, and chronic cholecystitis.[19,20] It has a highly effective antibacterial effect by acting on penicillin-binding proteins and inhibiting the synthesis of gram-positive, gram-negative and anaerobic bacteria.[20]

For children with pediatric bronchopneumonia, Edelstein et al found that piperacillin tazobactam combined with erythromycin could be effective in increasing immunoglobulin levels, decreasing inflammatory factors, and improving a treatment's efficacy.[21] Perry et al indicated that amikacin combined with piperacillin tazobactam sodium could effectively treat severe pneumonia in older adults.[22]

Wang et al confirmed that nebulized inhaled amikacin, combined with intravenous, piperacillin tazobactam sodium, was effective in reducing inflammatory factors in older patients with severe community-acquired pneumonia, with significant efficacy.[23] Rabby et al pointed out that the clinical efficacy of piperacillin sodium tazobactam sodium, combined with Xiyampin, in the treatment of severe pneumonia in older adults elderly, was precise, and it could significantly improve pulmonary ventilation and reduce the degree of inflammation with a high safety profile.[24]

Currently, few clinical studies have occurred on piperacillin tazobactam in combination with HFCWO to produce sputum excretion for the treatment of pneumonia during AE-COPD. Therefore, the current study intended to investigate the effectiveness and safety of piperacillin tazobactam in combination with the use of sputum removal using HFCWO to produce expectoration for the treatment of pneumonia in patients with AE-COPD and to provide a reference for clinical treatment.

MATERIALS AND METHODS

Participants

The research team designed a prospective, randomized controlled trial. The study took place at the Sixth Hospital of Wuhan of the Affiliated Hospital of Jianghan University in Wuhan, China. Potential participants were patients who had

been admitted to the hospital between January 2020 and November 2021 with AE-COPD combined with pneumonia.

Potential participants were included in the study if they: (1) met the diagnostic criteria for AE-COPD in the *Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease*[25] and for pneumonia in the *Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia in Adults in China*[26]; (2) had audible wet rales on lung auscultation, elevated leukocyte or neutrophil counts on laboratory tests, and chest radiograph findings of increased texture or infiltrative inflammatory lesions in both lungs; (3) had not inhaled or taken glucocorticoids within the month prior to the study; and (4) had no contraindications to the use of a sputum expeller.

Potential participants were excluded from the study if they: (1) had other inflammatory diseases in combination with COPD and pneumonia; (2) had lung cancer or other conditions with distinctive pathological manifestations; (3) had an infectious disease such as AIDS; (4) had sepsis or other serious infectious diseases in combination with COPD and pneumonia; (5) had severe, primary heart, liver, or kidney diseases; (6) had an allergy to the study's drug; (7) had unfixed head or neck trauma; (8) wouldn't be able to cooperate with oscillation or vibration; (9) had impaired consciousness; or (10) had combined lung abscess and bronchiectasis.

All patients gave informed consent and signed a written informed consent form.

Procedures

Randomization. Using the random number table method, the research team randomly assigned participants to one of two groups, an intervention group or a control group, each with 46 participants.

Intervention. After admission, both groups received conventional treatment with routine oxygenation, antibiotics, antispasmodics, antiasthmatic drugs, and phlegmolytic drugs as well as HFCWO for sputum removal. In addition to those treatments, the intervention group also received piperacillin tazobactam.

HFCWO for expectoration. The HFCWO used a V15 manufactured by Zhuhai Black Horse Medical Instrument (Zhuhai, Guangdong, China). The equipment consisted of two tubes connected to an inflatable undershirt at one end and to a small, pneumatic pulse generator at the other end. Through an intelligent electric switch, the pneumatic pulse generator rapidly inflated and deflated the undershirt in rotation, thus causing the undershirt to produce up to 20 compressions per minure and releases on the chest wall and finally producing an oscillating effect on the participant's chest wall for 20min/time for 2 times/d.

Piperacillin tazobactam. The research team purchased the drug from Zhuhai Federal Pharmaceutical (Zhuhai, Guangdong, China), product lot number: 0A083110, on the basis of treatment in the control group.

Outcome measures. The research team measured the treatment's efficacy at one day postintervention and evaluated clinical symptoms—the time of disappearance of clinical symptoms and calculated the length of hospital stay.

At baseline and at one day postintervention, the team also measured pulmonary function, laboratory indexes, and blood-gas-analysis indexes. The measurement of lung function used a German Jäger spirometer (Berlin, Germany). For the laboratory indexes, the research team collected 5ml of venous from participants, centrifuged it at 3000 r/min for 15 min, and extracted the upper serum to measure inflammatory responses using an enzyme-linked immunosorbent assay (ELISA). For the blood-gas analysis, the research team collected 5 ml of venous blood from participants and performed the test using an ABL80 automatic blood gas analyzer from Radiometer Denmark.

Finally, the research team evaluated the treatment's safety.

Intervention

The 2.25 g of piperacillin tazobactam was administered intravenously after sufficient dilution in 250 mL of a 5% dextrose, 2 times/d.

Outcome Measures

Efficacy. The research team measured participants' clinical symptoms, such as shortness of breath, chest tightness, and dyspnea; number of pulmonary rales, sputum volume, and values of various indicators of pulmonary function and blood gas. This measure included four categories: (1) cure—disappearance of clinical symptoms, no evidence of pulmonary rales, decreased sputum volume and thin sputum, and a return to normal for the pulmonary indicators; (2) effective—significant improvement in clinical symptoms, significant decrease in pulmonary rales, decrease in sputum volume, and a return to normal for the pulmonary indicators; (3) effective— improvement in clinical symptoms, improvement in the lung rales, decrease in sputum volume, and improvement in lung function and blood- gas indexes but not a return to normal; and (4) ineffective—none of the indexes had changed significantly or worsened.

Clinical symptoms. The evaluation of clinical symptoms included the time of disappearance of cough, sputum, dyspnea, and pulmonary rales.

Pulmonary function. The tests included measurements of one second(s) forceful expiratory volume (FEV1), forced vital capacity (FVC), FEV1 as a percentage of expected value (FEV1%), and FEV1/FVC.

Laboratory indexes. The testing included measurement of IL-2, IL-10, TNF-α, CRP, and PCT.

Blood-gas-analysis index. The testing included measurement of the levels of partial pressure of carbon dioxide (PaCO2), partial pressure of oxygen (PaO2), and arterial oxygen saturation (SaO2).

Safety analysis. The research team recorded all of participants' adverse reactions, such as nausea and decreased appetite during the treatment, and assessed their routine blood and urine and liver and kidney functions.

Table 1. Comparison of Demographics at Baseline Between the Intervention and Control Groups (N = 92)

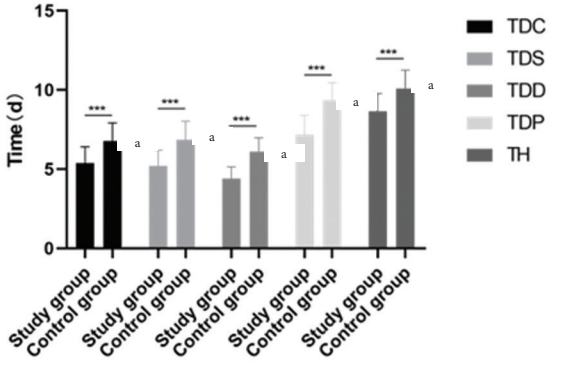
Group	Intervention Group n = 46 n (%) Mean ± SD	Control Group n = 46 n (%) Mean ± SD	χ^2/t	*P* value
Gender			0.187	.666
Males	28 (60.87)	30 (65.22)		
Females	18 (39.13)	16 (34.78)		
Age, y	59.32 ± 12.09	59.29 ± 12.06	0.012	.990
COPD disease duration, y	4.58 ± 1.02	4.52 ± 1.09	0.273	.785
Duration of AE-COPD disease, d	2.82 ± 0.36	2.79 ± 0.35	0.405	.686
Duration of pneumonia, d	2.19 ± 0.33	2.11 ± 0.35	1.128	.262
Comorbidities				
Hypoproteinemia	4 (8.70)	6 (13.04)	0.449	.503
Pulmonary underlying disease	8 (17.39)	7 (15.22)	0.080	.778
Diabetes mellitus	4 (8.70)	6 (13.04)	0.449	.503
Renal insufficiency	5 (10.87)	3 (6.52)	0.548	.459
Heart Failure	13 (28.26)	12 (26.09)	0.055	.815
Coronary heart disease	19 (41.30)	15 (32.61)	0.746	.388
Cerebrovascular disease	19 (41.30)	14 (30.44)	0.181	.277

Table 2. Comparison of Clinical Efficacy at One Day Postintervention Between the Intervention and Control Groups (N = 92)

Group	Cured n (%)	Significantly n (%)	Effective n (%)	Ineffective n (%)	Total Efficiency Rate n (%)
Intervention group (n = 46)	29 (63.05)	10 (21.74)	6 (13.04)	1 (2.17)	45 (97.83)
Control group (n = 46)	17 (36.96)	12 (26.09)	8 (17.40)	9 (19.57)	37 (80.44)
χ^2					6.035
P value					.029[a]

[a]$P < .05$, indicating that the total efficiency rate for the intervention group was significantly higher than that of the control group

Figure 1. Comparison of the Disappearance Time of Clinical Symptoms and Hospitalization Time Between the Intervention and Control Groups



[a]$P < .001$, indicating that the intervention group had a significantly shorter TDC, TDS, TDD, TDP, and TH than the control group did

Abbreviations: TDC, time to disappearance of cough; TDD, time to disappearance of dyspnea; TDP, time to disappearance of pulmonary rales; TDS, time to disappearance of sputum; TH, time to hospitalization.

Statistical Analysis

The study used SPSS 20.0 statistical software (IBM Corp., Armonk, New York, USA) to analyze the data. The research team calculated the means ± standard deviations (SDs) of the measurement data and the count-data rates [n(%s)], using the chi-square χ^2 test. A $P < .05$ indicates that the difference was statistically significant.

RESULTS

Participants

The study included and analyzed the data of 92 participants, with 46 participants in each group. Table 1 shows the demographic data for the groups. The mean age of the intervention group was 59.32 ± 12.09, with 28 male and 18 female participants. The mean age of the control group was 59.29 ± 12.06, with 30 male and 16 female participants. No significant differences existed between the groups at baseline ($P > .05$).

Clinical Efficacy

Table 2 shows that the intervention group's clinical efficacy, at 97.83%, was significantly higher at one day postintervention than that of the control groups, at 82.61% ($P < .05$).

Clinical Symptoms and Hospitalization Time

Figure 1 shows that the intervention group's time to disappearance of cough, sputum, dyspnea, and pulmonary rales and the hospitalization time at one day postintervention were significantly shorter than those of the control group ($P < .001$).

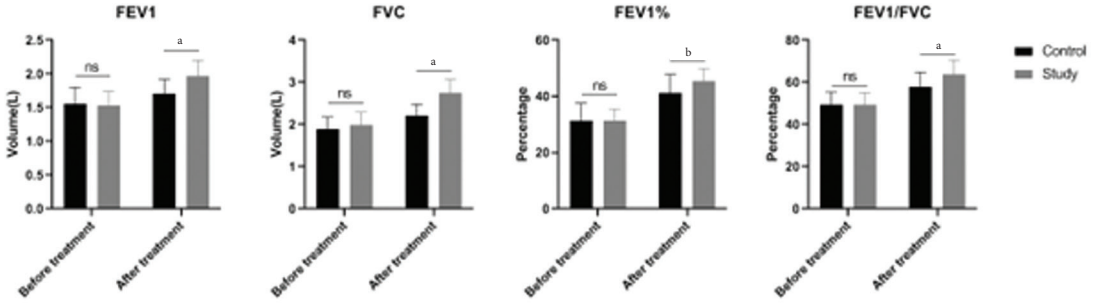
Pulmonary Function

Figure 2 shows that the two groups' FEV1, FVC, FEV1%, and FEV1/FVC levels weren't significantly different at baseline ($P > .05$). At one day postintervention, both groups' FEV1, FVC, FEV1%, and FEV1/FVC levels were higher than at baseline. The intervention group's FEV1 ($P < .0001$), FVC ($P < .0001$), FEV1% ($P < .001$), and FEV1/FVC ($P < .0001$) were significantly higher than those in the control group.

Laboratory Indexes

Figure 3 shows that the differences in the two groups' IL-2, IL-10, TNF-α, CRP, and PCT levels weren't significantly different at baseline ($P > .05$). At one day postintervention, both groups' IL-2 and IL-10 were higher and TNF-α, CRP, and PCT levels were lower than at baseline. The intervention group's IL-2 ($P < .0001$) and IL-10 ($P < .0001$) were significantly higher and TNF-α ($P < .0001$), CRP ($P < .01$), and PCT ($P < .0001$) were significantly lower than those in the control group ($P < .05$).

Figure 2. Comparison of Pulmonary Function Between the Intervention and Control Groups

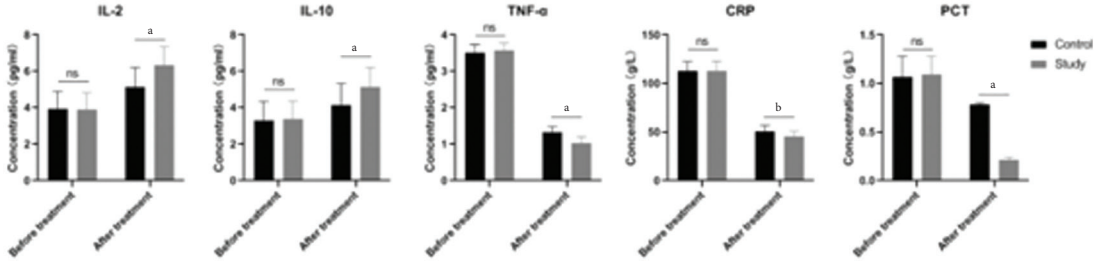


[a]$P < .0001$, indicating that the intervention group had a significantly higher FEV1, FVC, and FEV1%/ FVC postintervention than the control group did
[b]$P < .001$, indicating that the intervention group had a significantly higher FEV1% postintervention than the control group did

Note: ns Indicating no significant differences between the groups

Abbreviations: FEV1, one second forceful expiratory volume; FEV1%, FEV1 as a percentage of expected value; FVC, forced vital capacity.

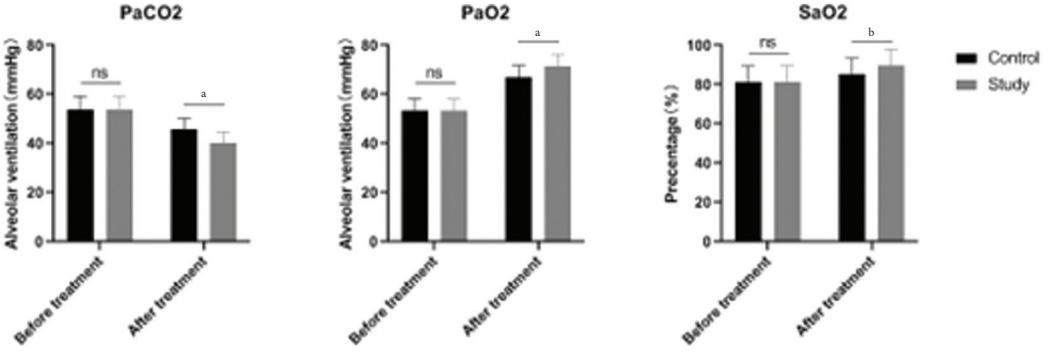
Figure 3. Comparison of Laboratory Indicators Between the Intervention and Control Groups



[a]$P < .0001$, indicating that the intervention group had significantly higher IL-2 and IL-10 and significantly lower TNF-α and PCT postintervention than the control group did
[b]$P < .01$, indicating that the intervention group had significantly lower CRP postintervention than the control group did

Abbreviations: CRP, C-reactive protein; IL-2, interleukin-2; IL-10, interleukin-10; PCT, procalcitonin; TNF-α, tumor necrosis factor-alpha.

Figure 4. Comparison of Blood Gas Analysis Between the Intervention and Control Groups



[a]$P < .0001$, indicating that the intervention group had significantly lower PaCO2 and significantly higher PaO2 postintervention than the control group did
[b]$P < .05$, indicating that the intervention group had significantly higher SaO2 postintervention than the control group did

Abbreviations: PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; SaO2, arterial oxygen saturation.

Blood Gas Analysis

Figure 4 shows that the two groups' PaCO2, PaO2, and SaO2 levels weren't significantly different at baseline ($P > .05$). At one day postintervention, both groups' PaCO2 had decreased and PaO2 and SaO2 had increased. The intervention group's PaCO2 was significantly lower than that of the control group ($P < .05$), but the intervention group's PaO2 and SaO2 levels were significantly higher than those in the control group (both $P < .0001$).

Safety Analysis

During the treatment, no adverse reactions occurred in the control group, and one participant had a decreased appetite occurred in the intervention group, showing an incidence of adverse reactions of 2.17% (data not shown). That participant received no special treatment, and the condition improved after stopping the drug. The difference in the incidence of adverse reactions wasn't statistically significant between the two groups ($P > .05$) In addition, at one day postintervention, all participants had normal levels in routine tests of blood and urine and liver and kidney functions.

DISCUSSION

The current study showed that the intervention group's clinical efficacy postintervention was significantly higher than that of the control group, and the time to disappearance of cough, sputum, dyspnea, and pulmonary rales and the length of hospitalization were significantly shorter in the intervention group than in the control group ($P < .05$). This suggests that piperacillin tazobactam combined with HFCWO to produce sputum removal can effectively improve the clinical efficacy of patients with AE-COPD combined with pneumonia, effectively relieve patients' clinical symptoms, shorten the disappearance time of clinical symptoms, and promote patients' recovery.

The current study showed that the intervention group's levels of IL-2 and IL-10 were significantly higher and of TNF-α, CRP, and PCT were significantly lower than those in the control group ($P < .05$). This suggests that piperacillin tazobactam combined with HFCWO to produce sputum removal can effectively increase the levels of IL-2 and IL-10 and decrease the levels of TNF-α, CRP, and PCT in patients with AE-COPD combined with pneumonia. This effect is conducive to improving patients' lung function and repairing damaged lung tissue.

The current research team further analyzed the safety of piperacillin tazobactam, and the incidence of adverse reactions in the two groups, and the difference in the incidence of adverse reactions wasn't statistically significant between the two groups ($P > .05$). Also, the routine blood and urine and liver and kidney functions were normal, suggesting that piperacillin tazobactam doesn't increase adverse reactions and is safe.

The current study had some shortcomings. All samples were collected from the research team's hospital, and the sample size included was small. The sample size should be expanded in other studies for further confirmation of the current study's findings.

CONCLUSIONS

Piperacillin tazobactam combined with HFCWO for sputum evacuation can effectively shorten the disappearance time of clinical symptoms and hospitalization time of patients who have AE-COPD combined with pneumonia; improve patients' pulmonary function; increase the IL-2 and IL-10 and decrease the TNF-α, CRP, and PCT levels; and regulate the blood-gas-analysis index, with few adverse effects and high safety. The therapy can be promoted for clinical applications.

AUTHORS' DISCLOSURE STATEMENT

The authors declare there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Li Li and Qiong Feng contributed equally to this paper.

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