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Original Article

Effect of bronchoalveolar lavage combined with high-dose ambroxol hydrochloride on severe pneumonia with respiratory failure

Hengping Zhang[1], Ren Liu[2]

[1]*Department of Pulmonary and Critical Care Medicine, Yueyang Central Hospital, Yueyang 414000, Hunan, China;* [2]*Department of Hematology, Yueyang Central Hospital, Yueyang 414000, Hunan, China*

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Abstract: Objective: To explore the effectiveness of bronchoalveolar lavage (BAL) combined with high-dose ambroxol hydrochloride (HD-AH) in geriatric patients with severe pneumonia (SP) and respiratory failure (RF). Methods: A retrospective analysis was conducted on 90 SP + RF patients. The control group (42 patients) received BAL with conventional-dose AH, while the observation group (48 patients) was treated with BAL + HD-AH. Clinical efficacy, symptom relief, postoperative recovery, pulmonary function, respiratory mechanics, arterial blood gas parameters, inflammatory markers, adverse events, incidence of multiple organ dysfunction syndrome (MODS), and overall mortality were compared. Results: The BAL + HD-AH therapy group showed superior outcomes, including a significantly higher total effective rate, faster symptom relief, improved postoperative recovery, better pulmonary function, enhanced respiratory mechanics, optimized arterial blood gas parameters, reduced inflammatory markers, and lower risks of MODS and mortality (all P<0.05). The safety profiles were similar (P>0.05). Conclusions: The BAL + HD-AH regimen is both safe and effective for elderly SP + RF patients, accelerating rehabilitation, reducing inflammation, improving pulmonary function and respiratory mechanics, optimizing blood gas parameters, and lowering MODS and mortality risks.

Keywords: Ambroxol hydrochloride, bronchoalveolar lavage, severe pneumonia, respiratory failure

Introduction

Pneumonia is a common clinical respiratory disease and a leading cause of hospitalization and mortality among patients [1]. Older adults are more difficult to treat than younger individuals due to factors such as impaired mucociliary clearance, weakened immune systems, and underlying comorbidities [2]. In 2015, pneumonia led to hospitalization of 6.8 million older adults globally, with approximately 1.1 million deaths during hospitalization [3]. Severe pneumonia (SP) represents a more critical form of the disease and requires a more aggressive and comprehensive treatment approach. Respiratory failure (RF), a frequent complication of SP, is characterized by impaired gas exchange between the lungs and the blood [4]. Its onset indicates that a lung infection has caused significant physiological dysfunction, necessitating immediate and intensive intervention. SP patients often have large amounts of viscous sputum in the respiratory tract, with reduced self-expectoration capability due to limited mobility. When thick sputum obstructs the airways, patients may experience significant dyspnea, impaired pulmonary ventilation, and gas exchange, potentially leading to death from RF in severe cases [5, 6]. Therefore, in addition to addressing the underlying cause, timely removal of sputum is crucial for alleviating symptoms such as dyspnea and improving the prognosis of SP patients.

Bronchoalveolar lavage (BAL) is an innovative technique based on fiberoptic bronchoscopy, enabling the rapid and effective removal of airway mucus, improving airway ventilation, allowing inhaled medications to directly contact the airway walls, and reducing inflammation [7]. Studies have demonstrated that BAL significantly controls the inflammatory status of SP patients, improves blood gas levels, and enhances treatment effectiveness [8]. Ambroxol

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hydrochloride (AH) is an expectorant used to treat respiratory diseases related to abnormal mucus secretion and impaired mucus transport. It promotes mucus clearance, facilitates sputum expectoration, relieves cough, and controls inflammation [9]. AH is available in various forms, including intramuscular and intravenous solutions, suppositories, syrups, granules, tablets, capsules, sustained-release oral formulations, and nebulized solutions [10]. Its simplicity of use, low cost, and high safety profile contribute to its widespread application. This study aims to evaluate the efficacy and safety of combining BAL with AH in treating SP patients complicated by RF, with the goal of providing a safer and more effective treatment option for these patients.

Materials and methods

Study population

This study employed a retrospective design. Ninety SP + RF patients who visited Yueyang Central Hospital between February 2023 and January 2024 were enrolled and divided into two groups based on treatment methods. The control group (42 cases) received BAL with conventional-dose AH, while the observation group (48 cases) was treated with BAL + HD-AH.

Inclusion criteria: Patients met the diagnostic criteria for pneumonia and RF [11, 12]; diagnosis confirmed by imaging, blood tests, and bacteriological culture; age ≥65; arterial partial pressure of oxygen (PaO_2) ≤60 mmHg; mechanical ventilation use; voluntary provision of signed informed consent.

Exclusion criteria: Presence of other infectious diseases, malignant tumors, other major organ failure, concomitant asthma or other respiratory diseases, contraindications to bronchoscopy, or history of allergic reactions to the study drugs. No significant inter-group differences were observed in sex, age, disease duration, RF type, and other general characteristics. The study was approved by the Yueyang Central Hospital Ethics Committee.

Treatment

Both groups received symptomatic treatments, including anti-infection therapy, cough relief, asthma relief, oxygen inhalation, electrolyte correction, mechanical ventilation, and nutritional support. The control group underwent BAL in addition to routine treatment. Patients fasted and were water-deprived for 6 hours before the procedure and were closely monitored for changes in arterial oxygen saturation (SaO_2). After local anesthesia, a fiberoptic bronchoscope was inserted through the nasal cavity into the airway. The affected lung segments with severe inflammation were identified using preoperative imaging, and vacuum aspiration was performed after lavage with 37°C normal saline. The lavage procedure was repeated three times (≤2.0 ml/kg per lavage), with a total procedure time of approximately 10 minutes. For patients with confirmed drug allergies (via drug susceptibility tests), 20 ml of sensitive antibiotics (vancomycin 15 mg/kg every 12 hours) were administered. For patients without allergies, 20 ml of broad-spectrum antibiotics (ceftriaxone 2 g every 12 hours + azithromycin 500 mg every 24 hours) was used, with the infusion maintained for at least 15 minutes before suctioning. The fiberoptic bronchoscope was removed slowly after the procedure. If the SaO_2 decreased abnormally during the procedure, the operation was halted, and supplemental oxygen was administered in the supine position until SaO_2 normalized. Additionally, 30 mg of AH injection (Shanghai Boehringer Ingelheim Pharmaceutical Co. Ltd., State Drug Approval Document Number: 20080083) was added to 100 ml of 0.9% sodium chloride injection for intravenous infusion twice a day. In the observation group, the AH dose was increased to 60 mg, with both groups receiving treatment for 7 days. The CT scans of the observation group before and after treatment are shown in **Figure 1**.

Endpoints

Clinical efficacy was evaluated at the end of treatment [13]: Cure: Cough, fever, and other symptoms disappeared; white blood cell count and classification normalized; absorption of lung lesions >90%. Marked efficacy: Cough, fever, and other symptoms were significantly alleviated; white blood cell count and classification normalized; absorption of lung lesions >50%. Effective: Symptoms such as fever and cough were partially improved; white blood cell count and classification normalized; absorption of lung lesions <50%. Ineffective: The above criteria were not met.

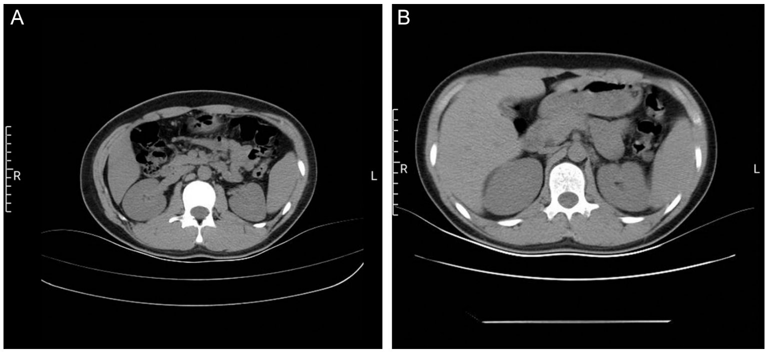

Figure 1. Representative pre- and post-treatment mediastinal window chest CT scans from both groups. A: Pre-treatment CT of the patient shows multiple patchy and nodular opacities in both lungs, as well as interlobular septal thickening in both lungs. B: Following bronchoscopic alveolar lavage + ambroxol hydrochloride therapy, the patient showed significant resolution of pulmonary lesions along with reduced bilateral pleural effusion compared to baseline.

The total effective rate was calculated as: Total effective rate = (cure + marked effectiveness) cases/total cases * 100%.

The time to remission of major clinical symptoms (lung rales, fever, cough), antimicrobial drug usage, ICU stay, and mechanical ventilation duration were recorded [14].

Postoperative recovery data included hospital stay length and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at one week post-treatment [15]. The APACHE II score ranges from 0 to 71, with higher values indicating greater disease severity and mortality risk.

Arterial blood samples (3 mL) were collected before and 7 days post-treatment for the measurement of SaO_2, PaO_2, and partial pressure of carbon dioxide ($PaCO_2$) using a blood gas analyzer (Wuhan Ali Road Medical Equipment Co., Ltd.) [16].

Lung function tests were conducted before and after treatment (7 days post-surgery) using a lung function detector, including peak expiratory flow (PEF), forced expiratory volume in 1s (FEV1), and the FEV1 to forced vital capacity (FVC) ratio (FEV1/FVC) [17].

Respiratory mechanics indices - airway resistance (RaW) and peak inspiratory pressure (PIP) - were assessed using an advanced ventilator before treatment initiation and 7 days after surgery [18].

Serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured before and after treatment (7 days post-surgery) by enzyme-linked immunosorbent assay (ELISA), and C-reactive protein (CRP) levels were assessed by immunonephelometry using 5 mL of morning venous blood collected from both groups [19].

Adverse reactions during treatment were recorded for both groups [20].

The incidence of multiple organ dysfunction syndrome (MODS) and mortality rates during treatment were documented for both groups [21].

Statistical analyses

Data were processed and visualized using GraphPad Prism 7. The Chi-square test was used for comparisons of categorical data, which are typically represented by frequency or percentage. Independent t-tests were used for inter-group comparisons of measurement data which are represented by mean and standard deviation. Paired t-tests were used for intra-group comparisons before and after treatment. Differences were considered statistically significant when *P*-values were <0.05. Using Fleiss' continuity-adjusted calculation with predefined parameters (P_1=0.70, P_2=0.85; two-tailed α=0.05, β=0.25), the minimum sample size required for each group was 37 cases. The final allocation (control: 42, observation: 48) exceeded this threshold.

Results

Comparison of baseline characteristics

The control and observation groups demonstrated comparable baseline characteristics, with no statistically significant differences (all P>0.05) in gender distribution, age, disease duration, body weight, or family history (**Table 1**).

Comparison of clinical efficacy

As shown in **Table 2**, the observation group demonstrated a higher total clinical efficacy

Table 1. Comparison of baseline characteristics

Groups	Control group (n=42)	Observation group (n=48)	χ^2	P
Gender			0.550	0.458
Male	26 (61.90)	26 (54.17)		
Female	16 (38.10)	22 (45.83)		
Age (years)	66.86±5.32	66.94±7.77	0.056	0.955
Disease duration (years)	1.95±0.94	2.31±1.27	1.510	0.135
Body weight (kg)	69.24±18.42	61.23±21.06	1.908	0.060
Family history			2.893	0.089
Without	32 (76.19)	43 (89.58)		
With	10 (23.81)	5 (10.42)		

Table 2. Comparison of clinical efficacy [n (%)]

Groups	Cure	Marked effectiveness	Effectiveness	Ineffectiveness	Total effective rate
Control group (n=42)	2 (4.76)	15 (35.71)	15 (35.71)	10 (23.81)	32 (76.19)
Observation group (n=48)	8 (16.67)	24 (50.00)	13 (27.08)	3 (6.25)	45 (93.75)
χ^2					5.589
P					0.018

Table 3. Comparison of clinical indexes ($\bar{x}$±sd, d)

Groups	Control group (n=42)	Observation group (n=48)	t	P
Cough remission time	16.11±3.74	13.08±3.91	3.743	<0.001
Lung rale remission time	10.90±3.21	7.92±3.04	4.520	<0.001
Fever remission time	9.64±2.13	7.25±2.33	5.052	<0.001
Antimicrobial use time	9.29±2.50	6.90±2.07	4.960	<0.001
Mechanical ventilation time	10.10±2.77	8.58±2.08	2.965	0.004
Duration of ICU stay	12.07±2.67	10.60±2.77	2.554	0.012

rate compared to the control group (93.75% vs. 76.19%, P<0.05).

Comparison of clinical indicators

The duration of clinical symptom remission (including cough, lung rales, and fever), antimicrobial drug usage, mechanical ventilation duration, and ICU stay were all significantly shorter in the observation group compared to the control group (all P<0.05). Detailed data are presented in **Table 3**.

Comparison of postoperative recovery indicators

The observation group exhibited significantly shorter hospital stays and lower APACHE II scores at one week post-treatment compared to the control group (P<0.01). Detailed results are shown in **Table 4**.

Comparison of blood gas parameters

Before treatment, PaO_2, $PaCO_2$, and SaO_2 levels did not differ significantly between the two groups (all P>0.05). After treatment, both groups showed an increase in PaO_2 and SaO_2, and a decrease in $PaCO_2$ (all P<0.05). The observation group showed even higher PaO_2 and SaO_2 levels and a lower $PaCO_2$ (all P<0.05). See **Figure 2**.

Comparison of pulmonary function indexes

As shown in **Figure 3**, pre-treatment levels of PEF, FVC1, and FVC1/FVC were similar between the groups (all P>0.05). Both groups showed an increase in PEF, FVC1, and FVC1/FVC post-treatment (all P<0.05), with a more marked improvement in the observation group (all P<0.05).

Table 4. Comparison of postoperative recovery indicators ($\bar{x}\pm s$, d)

Groups	Control group (n=42)	Observation group (n=48)	t	P
Length of hospital stay (d)	18.95±3.67	16.19±3.17	3.828	<0.001
APACHE II scores at one week post-treatment (points)	15.02±4.84	12.50±3.72	2.788	0.007

Note: APACHE II, Acute Physiology and Chronic Health Evaluation II.

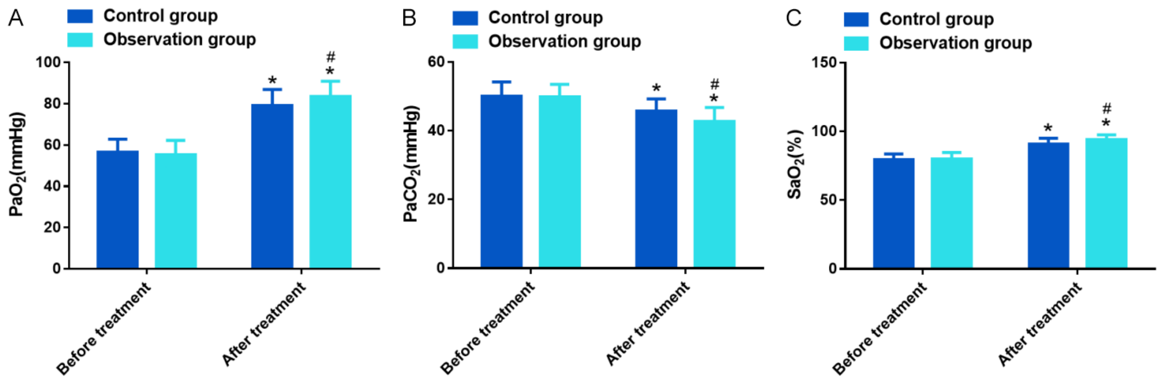

Figure 2. Comparison of blood gas parameters. A: Comparison of changes in PaO_2. B: Comparison of changes in $PaCO_2$. C: Comparison of changes in SaO_2. Note: PaO_2, arterial partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, arterial oxygen saturation. *P<0.05 vs. before treatment within the group; #P<0.05 vs. the control group at the same time point.

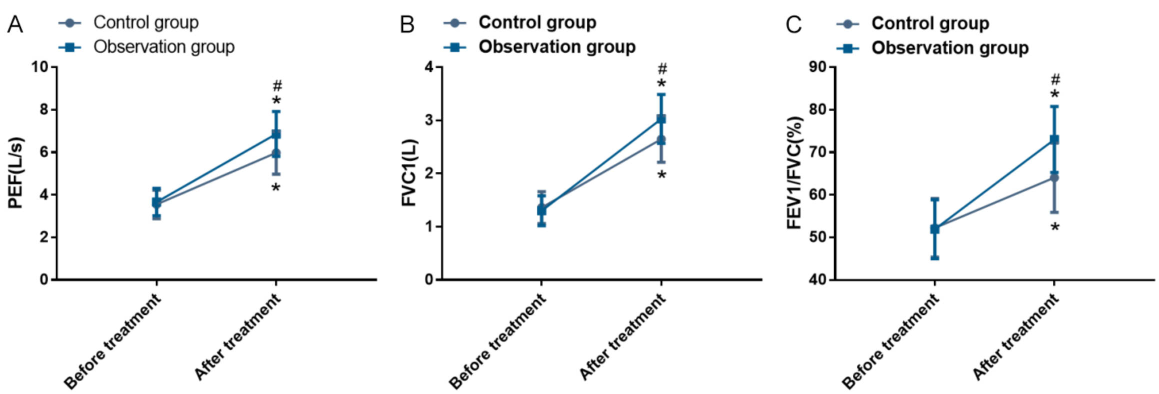

Figure 3. Comparison of pulmonary function indexes. A: Comparison of PEF changes before and after treatment. B: Comparison of changes in FVC1 before and after treatment. C: Comparison of changes in FEV1/FVC before and after treatment. Note: PEF, peak expiratory flow; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity. *P<0.05 *vs.* before treatment within the group; #P<0.05 *vs.* the control group at the same time point.

Comparison of respiratory mechanics indices

No significant baseline differences were observed in RaW and PIP between the groups (both P>0.05). After treatment, both groups exhibited significant reductions in RaW and PIP (both P<0.05). Notably, the observation group showed significantly lower post-treatment values for both parameters compared to the control group (both P<0.05, **Figure 4**).

Comparison of serum levels of inflammatory factors

As indicated in **Figure 5**, there were no significant differences in CRP, TNF-α, and IL-6 levels between the groups before treatment (all P>0.05). After treatment, CRP, TNF-α, and IL-6 levels decreased in both groups (all P<0.05), with a more substantial reduction in the observation group (all P<0.05).

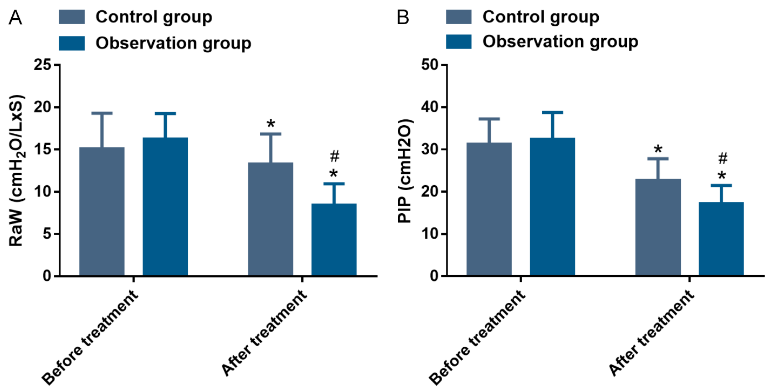

Figure 4. Comparison of respiratory mechanics indices. A: Changes in RaW before and after treatment in the two groups. B: Changes in PIP before and after treatment in the two groups. Note: RaW, airway resistance; PIP, peak inspiratory pressure. *P<0.05 versus pretreatment values within the same group; #P<0.05 versus control group at corresponding time points.

Comparison of adverse reactions

Both groups experienced some adverse reactions, but there were no significant inter-group differences (P>0.05, **Table 5**).

Comparison of MODS incidence and mortality rates

The observation group had significantly lower rates of both MODS and mortality compared to the control group (both P<0.05, **Table 6**).

Discussion

Pneumonia can trigger both local and systemic inflammatory responses, with excessive or uncontrolled inflammation leading to lung tissue damage that disrupts gas exchange and results in RF [22]. In SP + RF patients, sputum tends to become excessively viscous and difficult to expel due to increased airway resistance, which leads to severe airway obstruction [6]. Therefore, maintaining airway patency is crucial for promoting lung function recovery in such patients. Currently, widely used expectoration strategies include expectorants, postural drainage techniques, and sputum suction via suction tubes, although no standard protocol has yet been established.

The BAL technique involves multiple lavages of the affected area via fiberoptic bronchoscopy, aimed at effectively removing deposits and inflammatory emissions from the alveoli, thereby improving respiratory function [23]. When used in SP patients, BAL effectively clears the respiratory tract and lung secretions, restores normal lung ventilation, and facilitates the collection of lung samples for bacteriological analysis, which provides a scientific basis for personalized antimicrobial therapy [24]. AH, a commonly used expectorant, helps dilute sputum by decomposing glycoproteins in polysaccharide fibers. Additionally, it enhances the efficiency of airway cilia movement, reduces sputum accumulation in the airways, and alleviates cough symptoms [25]. Typically, AH, combined with posture changes and back slapping, can promote sputum clearance from the upper respiratory tract. However, it is less effective in cleaning sputum located below the secondary bronchus, particularly when the sputum is thick and viscous, forming a sputum scab in the airways.

In this study, the observation group demonstrated superior clinical outcomes compared to the control group, achieving a higher overall treatment efficacy rate, along with significantly faster symptom relief, shorter durations of antibiotic therapy and mechanical ventilation, and reduced ICU and hospital stays. Furthermore, the observation group exhibited higher post-treatment PaO_2, SaO_2, PEF, FVC1, and FVC1/FVC, and lower $PaCO_2$, RaW, and PIP values compared to the control group. These findings suggest that compared to conventional doses, the combination of high-dose HD-AH and BAL enhances clinical efficacy in SP + RF patients, facilitating early restoration of normal pulmonary ventilation and improving respiratory function. The following reasons can explain these results: First, the therapeutic effect of AH increases with dosage [26]. Higher AH concentrations in the lungs lead to a stronger affinity of lung tissue for the drug, thus enhancing its efficacy. Second, HD-AH increases the concentration of several antibiotics in bronchopulmonary tissue, significantly raising their levels in bronchial secretions and prolonging their retention in lung tissue [27].

Research by Meng et al. [28] showed that BAL with AH significantly improved clinical out-

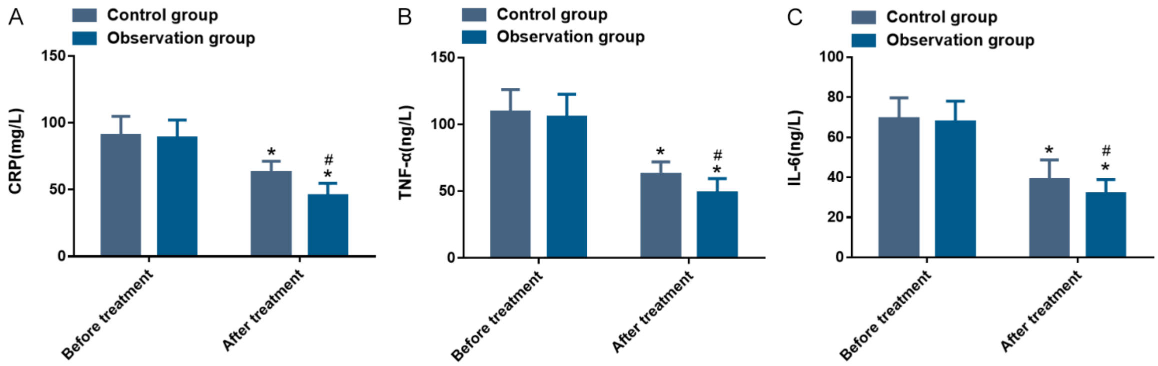

Figure 5. Comparison of serum inflammatory factors. A: Comparison of changes in CRP. B: Comparison of changes in TNF-α. C: Comparison of changes in IL-6. Note: CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6. *P<0.05 *vs.* before treatment within the group; #P<0.05 *vs.* the control group at the same time point.

Table 5. Comparison of adverse reactions [n (%)]

Groups	Control group (n=42)	Observation group (n=48)	χ^2	P
Dizziness and fatigue	1 (2.38)	2 (4.17)		
Nausea and vomiting	1 (2.38)	2 (4.17)		
Arrhythmia	1 (2.38)	1 (2.08)		
Chest tightness	0 (0.00)	1 (2.08)		
Rash	1 (2.38)	1 (2.08)		
Total occurrence	4 (9.52)	7 (14.58)	0.534	0.465

Table 6. Comparison of MODS incidence and mortality rates [n (%)]

Groups	Control group (n=42)	Observation group (n=48)	χ^2	P
MODS	10 (23.81)	4 (8.33)	4.084	0.043
Mortality	9 (21.43)	3 (6.25)	4.466	0.035

Note: MODS, multiple organ dysfunction syndrome.

comes in cerebral infarction cases, with no marked increase in adverse reactions compared to standalone ambroxol use, which aligns with our findings. Additionally, Li et al. [29] demonstrated that AH, as an adjunct in elderly chronic obstructive pulmonary disease patients, improved therapeutic outcomes beyond standard care, enhanced pulmonary metrics, boosted immunity, and suppressed pro-inflammatory cytokines (IL-6, IL-8, TNF-α), supporting the current study's results.

Pneumonia can trigger systemic inflammatory responses, which may lead to severe complications such as systemic inflammatory response syndrome, shock, and multiple organ failure [30]. Cytokines play a crucial regulatory role in pneumonia by modulating inflammation and influencing the recruitment and activation of immune cells to fight pathogens [31]. However, excessive release of inflammatory mediators can result in extensive tissue damage and organ dysfunction [32]. CRP is an acute-phase protein produced by the liver and is commonly used to assess infection and inflammation levels, with higher levels indicating more severe infection and inflammation [33].

The results of this study showed a reduction in CRP, TNF-α, and IL-6 levels in both groups after treatment, with the observation group demonstrating lower levels of these inflammatory markers compared to the control group. This indicates that the high hyperinflammatory status in elderly patients with SP + RF was alleviated following HD-AH plus BAL treatment, improving patient outcomes. Consistent with our data, prior research by Wang et al. [34] demonstrated that HD-AH administration in SP patients significantly enhanced lung function, reduced inflammatory markers, and accelerated infection resolution, ICU discharge, and overall hospitalization duration, complementing our findings.

At the end of this study, we systematically evaluated the incidence of adverse reactions, MODS, and mortality in both groups during treatment. The results were highly encouraging: HD-AH combined with BAL therapy demonstrated an excellent safety profile, with no severe adverse reactions and no significant increase in overall adverse event rates. Additionally, this treatment regimen was associated with significantly lower rates of MODS and mortality, suggesting its potential efficacy in preventing these critical complications. In agreement with Tang et al. [35], combining AH with fiberoptic bronchoscopy in elderly SP patients has proven effective in improving blood gas indicators and reducing mortality, which aligns with the conclusions of the current study.

This investigation introduces several novel aspects: Firstly, it establishes the combination of BAL and HD-AH as a reliable intervention for elderly SP patients with concurrent RF, demonstrating both therapeutic potential and procedural safety. Secondly, it comprehensively presents the clinical benefits of this treatment for elderly SP + RF patients from multiple perspectives, including clinical symptom relief, postoperative recovery, lung function, respiratory mechanics, blood gas parameters, inflammation, MODS, and mortality. This provides robust clinical evidence supporting the adoption of BAL + HD-AH in this patient population.

Overall, the implementation of HD-AH combined with BAL therapy in elderly SP + RF patients demonstrates significant clinical benefits. This regimen effectively clears airway secretions, promotes postoperative recovery, reduces systemic inflammation, and improves parameters in blood gas analysis, pulmonary function, and respiratory performance. Importantly, it serves as a protective intervention against MODS and mortality, highlighting its substantial clinical value in managing this high-risk patient population. However, some limitations exist in this research. First, all subjects were from the same hospital, which may introduce regional bias. Second, the study focused on patients over 65 years old, limiting the generalizability of findings to other age groups. Finally, while this study confirms the safety of HD-AH in elderly patients with SP and RF, the safety of long-term high-dose use remains to be established.

Disclosure of conflict of interest

None.

Address correspondence to: Ren Liu, Department of Hematology, Yueyang Central Hospital, No. 39 Dongmaoling Road, Yueyang 414000, Hunan, China. Tel: +86-0730-8246001; E-mail: liuren68@hotmail.com

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