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Original Article

Effect of blood purification combined with antibiotics on CC-16 and SP-D levels and prognosis in patients with severe acute pancreatitis complicated by acute respiratory distress syndrome

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Abstract: Objective: To investigate the effects of continuous blood purification (CBP) combined with antibiotics on pulmonary surfactant protein D (SP-D), Clara cell protein-16 (CC-16), and prognosis in patients with severe acute pancreatitis (SAP) complicated by acute respiratory distress syndrome (ARDS). Methods: A total of 128 patients with SAP and ARDS treated at Fudan University Shanghai Cancer Center from June 2021 to June 2023 were enrolled. Patients were divided into two groups: a control group (n=64) receiving routine treatment (gastrointestinal decompression, somatostatin administration, nutritional support, correction of water-electrolyte imbalance, and microcirculation improvement) and an observation group (n=64) treated with CBP combined with antibiotics. Clinical data, including the pancreatic edema resolution time, ventilator weaning time, and hospital stay, were compared between groups. Additional comparisons included intra-abdominal pressure (IAP), blood amylase (AMS), urinary amylase (UAMY), inflammatory markers [tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β)], respiratory mechanics indices [airway peak pressure (Peak), airway plateau pressure (Plat), respiratory rate (F)], and blood oxygen levels [partial pressure of arterial oxygen (PaO_2), PaO_2/fraction of inspired oxygen (FiO_2)] before and after treatment. Results: The observation group demonstrated significantly better outcomes compared to the control group in terms of pancreatic edema resolution time, ventilator weaning time, hospital stay, and other indicators (all P<0.05). The 28-day mortality rate in the observation group was significantly lower than in the control group (P<0.05). Post-treatment levels of CC-16, SP-D, Peak, Plat, and other indicators improved significantly in both groups compared to baseline (all P<0.05). The observation group exhibited significantly greater improvements in PaO_2 and PaO_2/FiO_2 compared to the control group (all P<0.05). Conclusion: CBP combined with antibiotics significantly improves clinical symptoms, reduces inflammatory markers, enhances prognosis, and lowers mortality rates in patients with SAP complicated by ARDS.

Keywords: Severe acute pancreatitis, prognosis, blood purification, pulmonary surfactant protein D, Clara cell protein-16

Introduction

In clinical practice, medical staff frequently encounter patients with severe acute pancreatitis (SAP), a condition with complex etiology. SAP presents with clinical manifestations such as abdominal pain, abdominal distension, vomiting, nausea, and fever [1]. Among the complications of SAP, acute respiratory distress syndrome (ARDS) is particularly severe, as it can exacerbate the patient's condition, causing lung damage and potentially progressing to respiratory failure or multiple organ failure within 72 hours. Once ARDS occurs, the mortality rate can reach up to 50% [2].

Non-invasive mechanical ventilation can alleviate hypoxia to some extent; however, it does not fully address the hemodynamic disorders associated with SAP-induced ARDS [3]. Studies have demonstrated that an uncontrolled inflammatory response is a key driver of ARDS in SAP

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Table 1. Comparison of baseline characteristics between the two groups

Factor		Control group (n=64)	Observation group (n=64)	$Z/\chi^2/t$	P
Gender (male/female, n)		35/29	38/26	0.287	0.592
Age (years)		43.61±5.32	44.81±5.61	1.242	0.217
APACHE II score ($\bar{x} \pm s$)		33.78±6.08	35.03±5.76	1.194	0.235
Ranson score ($\bar{x} \pm s$)		8.61±1.49	8.09±1.48	1.800	0.074
Pathogeny	The bile origin (n)	25	22	0.900	0.826
	Excessive drinking (n)	19	17		
	High fat (n)	11	13		
	Other (n)	9	12		

Note: APACHE: Acute Physiology and Chronic Health Evaluation.

[4]. Patients experience reduced humoral and cellular immunity, release large amounts of toxic substances, and develop increased capillary permeability. This leads to reduced lung compliance, increased intrapulmonary shunting, and persistent hypoxemia with dyspnea. Early and effective treatment is therefore critical to improve respiratory function, restore fluid balance, and protect organ functions.

Continuous blood purification (CBP) employs high-efficiency, low-resistance filters to correct internal environmental disturbances, remove metabolic toxins, reduce inflammatory factors, restore immune regulation, and improve microcirculation. These effects collectively enhance patient prognosis [5]. Simultaneously, research suggests that [6] early use of broad-spectrum antibiotics capable of penetrating the blood-pancreatic barrier can effectively control infections and reduce mortality.

The clinical management of SAP complicated by ARDS remains a significant challenge due to the complexity of inflammatory processes involved. Current treatments, including supportive care, non-invasive mechanical ventilation, and broad-spectrum antibiotics, offer limited efficacy in severe cases [7].

To address this gap, this study innovatively investigated the combined effects of CBP and antibiotics in patients with SAP complicated by ARDS. By focusing on pulmonary surfactant protein D (SP-D) and Clara cell protein-16 (CC-16) levels, the study provides a novel perspective on how CBP combined with antibiotics can effectively manage inflammatory responses and improve clinical outcome. Specifically, this research explores the synergistic benefits of these treatments on biomarkers associated with lung injury and inflammation, suggesting a possibly superior therapeutic strategy. The findings aim to contribute to clinical practice guidelines, enhancing the management of these critically ill patients.

Materials and methods

Materials

A total of 128 patients with SAP complicated with ARDS who were treated at Fudan University Shanghai Cancer Center from June 2021 to June 2023 were included in this study. The patients were divided into two groups based on their treatment regimen: a control group (n=64) and an observation group (n=64).

Inclusion criteria: (1) Patients meeting the diagnostic criteria for SA and ARDS [8, 9]. (2) Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥20. (3) First-episode patients. (4) Patients who understood the study's objectives.

Exclusion criteria: (1) Patients with malignant tumor. (2) Patients undergoing surgical treatment for SAP. (3) Patients with upper gastrointestinal obstruction, perforation, or massive hemorrhage. (4) Patients with autoimmune diseases. (5) Patients with impaired vision, hearing, or mental state. (6) Patients with pulmonary infection or acute/chronic heart failure. (7) Patients with pancreatic encephalopathy or coma.

Baseline characteristics of the two groups are shown in **Table 1**. Statistical analysis of **Table 1** indicated no significant differences between the groups (P>0.05). This study was approved

by the Ethics Committee and Institutional Review Board of Fudan University Shanghai Cancer Center.

Methods

The control group received routine treatment, including gastrointestinal decompression, somatostatin administration, nutritional support, correction of water-electrolyte imbalance, and microcirculation improvement. Oxygen therapy was provided using a high-flow mask within six hours of admission. For patients with a partial pressure of oxygen (PaO_2) below 60 mmHg, noninvasive ventilatory support was delivered using a continuous positive airway pressure (CPAP) device (CPAP20, Shenyang Xinsong Medical Technology Co., Ltd.). The oxygen concentration ranged from 40% to 100%, with initial inspiratory pressures of 5-15 cmH_2O, expiratory pressures of 5-12 cmH_2O, and respiratory rates of 14-18 breaths per minute.

The observation group received routine treatment plus CBP combined with antibiotic therapy. Antibiotics included fluoroquinolones (X19-990263, Ranbaxy Laboratories Limited) plus metronidazole (H33021319, Wanbangde Pharmaceutical Group Co., Ltd.) or cephalosporins (H33020327, Zhejiang Ende Pharmaceutical Co., Ltd.) plus metronidazole (H33021319. Wanbangde Pharmaceutical Group Co., Ltd.) for 10-14 days [10]. CBP employed a hollow fiber hemodialysis filter (Ultraflux AV1000S, Fresenius AG, Germany).

For anticoagulation, low molecular weight heparin (H20052319, Shenzhen Saibaoer Biopharmaceutical Co., Ltd.) was used. The initial dose was 2000-4000 U, followed by a maintenance dose of 200-400 U/hour. Blood flow was maintained at 250-300 mL/min, and the replacement fluid flow rate was 4000 mL/hour, supplemented via pre-replacement.

Observation index

General patient information, including age, gender, etiology, and APACHE II scores, was collected upon admission.

Clinical data were compared and organized between the two groups [11], including the time required for pancreatic edema resolution time, ventilator weaning time, and hospital stay.

The levels of urinary amylase (UAMY), serum amylase (AMS), and intra-abdominal pressure (IAP) were compared between the two groups [12].

Urine and blood samples were collected before treatment and on the third day. AMS levels were measured using a fully automated biochemical analyzer (MERCK, Germany), and UAMY levels were determined using a semi-automatic analyzer (VITA-LAB-Micro, The Netherlands).

IAP levels were recorded before treatment and on the third day of treatment.

The levels of SP-D, CC-16, and inflammatory markers (e.g., IL-6 and IL-1β) were analyzed [13]. Venous blood samples were collected before and on the third day of treatment, centrifuged at 3000 r/min to remove sediment, and the serum was stored at -80°C. An enzyme-linked immunosorbent assay (ELISA) kit (BD, USA) was used to measure the levels of inflammatory factors.

The blood oxygen indices and respiratory mechanics (Peak, Plat, and F) were compared between the two groups [14].

A Dräger ventilator (Shanghai Dräger Medical Equipment Co., Ltd., Infinity C300, Germany) was used to measure Peak, Plat, and F before and on the third day of treatment.

Venous blood was collected, centrifuged, and serum stored at -20°C. A blood gas analyzer (OFMETECH, USA) was used to determine PaO_2 and PaO_2/FiO_2 levels. Each test was performed 3-5 times per patient, with an error margin between two tests under 5%. The best value was selected for statistical analysis.

Statistical methods

Statistical analysis was performed using SPSS 20.0.

Measured data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using the t-test.

Categorical data were expressed as percentages (%) and analyzed using the χ^2 test.

A *P*-value <0.05 was considered significant.

Table 2. Comparison of clinical outcomes and prognostic indicators between the two groups

Group	Length of stay (d)	Ventilator weaning time (d)	Time of improvement of abdominal pain and distension (d)	Pancreatic oedema resolution time (d)	28 d Mortality Rate (n, %)
Observation group (n=64)	17.18±5.74	2.72±0.91	3.17±0.70	5.72±1.23	3 (4.69%)
Control group (n=64)	27.95±5.49	4.42±1.17	4.05±0.72	8.25±1.05	11 (17.19%)
χ^2/t	10.848	9.175	7.011	12.515	5.133
P	<0.001	<0.001	<0.001	<0.001	0.023

Table 3. Comparison of IAP, AMS, and UAMY levels between the two groups before and after treatment (x ± s)

Group	IAP (mmHg)		AMS (U/L)		UAMY (U/L)	
	Before treatment	Post-treatment	Before treatment	Post-treatment	Before treatment	Post-treatment
Observation group (n=64)	19.39±3.23	11.83±3.62#	538.65±47.89	185.79±22.98#	750.43±52.58	267.69±21.98#
Control Group (n=64)	20.19±4.16	14.56±3.20#	534.52±44.05	266.94±28.26#	748.49±45.75	348.49±41.93#
t	1.215	4.520	0.508	17.823	0.223	13.654
P	0.227	<0.001	0.613	<0.001	0.824	<0.001

Note: Before comparison treatment, *P*<0.05 was represented by the symbol #. IAP: Intra-abdominal Pressure, AMS: Blood Amylase, UAMY: Urinary Amylase.

Results

Comparison of baseline characteristics

The baseline characteristics of the control and observation groups showed no significant differences, including gender distribution, age, APACHE II scores, Ranson scores, and etiological factors such as bile origin, excessive alcohol intake, high-fat diet, and other causes (all P>0.05 These results suggest the two groups were comparable (**Table 1**).

Comparison of the prognosis

The observation group exhibited significantly better clinical outcomes compared to the control group. Metrics such as pancreatic edema resolution time, ventilator weaning time, and hospital stay were notably shorter in the observation group (all P<0.05). Additionally, patients in the observation group showed faster improvement in abdominal pain and distension (P<0.05). The 28-day mortality rate was significantly lower in the observation group (4.69%) compared to the control group (17.19%) (P<0.05), indicating improved overall prognosis with CBP combined with antibiotics (**Table 2**).

Comparison of IAP, AMS, and UAMY levels

Post-treatment comparisons of IAP, AMS, and UAMY levels between the two groups revealed significant improvements in the observation group compared to the control group (all P<0.05) (**Table 3**; **Figure 1**).

Comparison of inflammatory factor levels

The levels of inflammatory factors, including TNF-α, IL-1β, and IL-6, were significantly lower in the observation group after treatment compared to the control group (all P<0.05) (**Table 4**; **Figure 2**).

Comparison of CC-16 and SP-D levels

The observation group showed significant improvements in CC-16 and SP-D levels after treatment compared to the control group (both P<0.05) (**Table 5**; **Figure 3**).

Comparison of respiratory mechanics and blood oxygen levels

Post-treatment comparisons of respiratory mechanics indicators, including Peak, Plat, and F, revealed significant improvements in the observation group compared to the control group (all P<0.05) (**Table 6**; **Figure 4**).

Discussion

Severe acute pancreatitis (SAP) is characterized by an acute onset and rapid progression, often influenced by multiple factors. Without

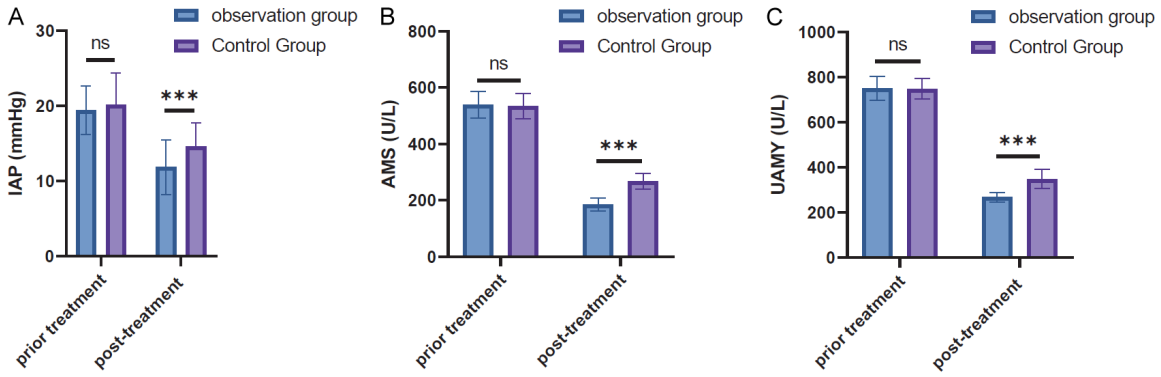

Figure 1. Changes in IAP, AMS, and UAMY levels in the two groups. A: IAP (mmHg); B: AMS (U/L); C: UAMY (U/L). IAP: Intra-abdominal Pressure, AMS: Blood Amylase, UAMY: Urinary Amylase. ns: No significant difference, ***: $P<0.001$.

Table 4. Comparison of inflammatory factor levels between the two groups before and after treatment (x ± s)

Group	IL-6 (pg/mL)		IL-1β (pg/mL)		TNF-α (ng/L)	
	Before treatment	Post-treatment	Before treatment	Post-treatment	Before treatment	Post-treatment
Control Group (n=64)	21.90±6.13	15.73±3.41#	297.51±29.21	237.54±24.78#	2.85±0.43	1.42±0.38#
Observation group (n=64)	21.24±5.68	10.59±3.12#	302.64±33.03	173.90±25.97#	2.87±0.72	0.68±0.19#
t	0.632	8.897	0.931	14.183	0.191	13.93
P	0.529	<0.001	0.354	<0.001	0.849	<0.001

Note: Before comparison treatment, $P<0.05$ was represented by the symbol #. IL-6: Interleukin-6, IL-1β: Interleukin-1 Beta, TNF-α: TNF-α.

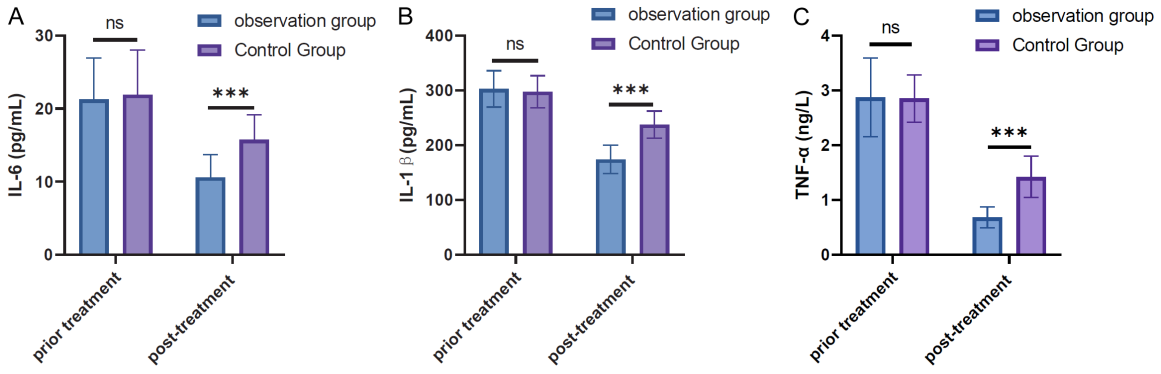

Figure 2. Changes in inflammatory factor levels in the two groups. A: IL-6 (pg/mL); B: IL-1β (pg/mL); C: TNF-α (ng/L). IL-6: Interleukin-6, IL-1β: Interleukin-1 Beta, TNF-α: TNF-α. ns: No significant difference, ***: $P<0.001$.

timely treatment, SAP poses a severe threat to patient survival. ARDS is a common and life-threatening complication. Hypoxemia caused by ARDS exacerbates tissue ischemia and hypoxia, intensifies the inflammatory response, and worsens the condition, making it challenging to manage. Therefore, effective clinical interventions are critical to reducing mortality rates [15].

With advances in SAP treatment, CBP, a non-surgical technique, has shown significant promise. CBP removes small molecular toxins and organic acids through continuous venovenous hemodiafiltration, eliminates pro-inflammatory and anti-inflammatory mediators, corrects acid-base imbalances, prevents pancreatic necrosis and infection, and improves the function of vital organs, including the heart,

Table 5. Comparison of SP-D and CC-16 levels between the two groups before and after treatment (x ± s)

Groups	SP-D (ng/L)		CC-16 (ng/L)	
	Before treatment	Post-treatment	Before treatment	Post-treatment
Control Group (n=64)	72.24±9.20	61.83±7.51#	52.97±13.34	45.75±7.98#
Observation group (n=64)	73.82±9.43	58.07±7.08#	53.99±12.06	42.91±6.42#
t	0.959	2.914	0.454	2.218
P	0.339	0.004	0.651	0.028

Note: Before comparison treatment, $P<0.05$ was represented by the symbol #. SP-D: Pulmonary Surfactant Protein D, CC-16: Clara Cell Protein-16.

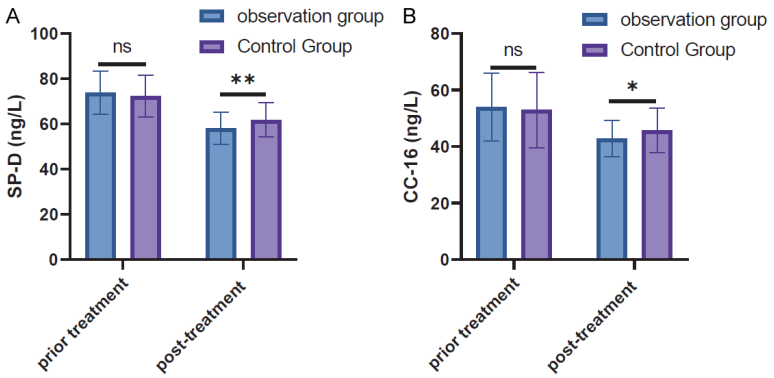

Figure 3. Changes in the two groups in SP-D levels and CC-16. A: SP-D (ng/L); B: CC-16 (ng/L). SP-D: Pulmonary Surfactant Protein D, CC-16: Clara Cell Protein-16. ns: No significant difference, *: $P<0.05$, **: $P<0.01$.

kidneys, liver, and brain [16]. Studies indicate that approximately 80% of SAP-related deaths are attributed to concurrent bacterial infections [17]. Research further demonstrates that early antibiotic administration can significantly reduce the risk of pancreatic infection [18]. Thus, this study applied CBP combined with antibiotics to treat SAP patients with ARDS to achieve better therapeutic outcomes.

AMS is an enzyme secreted by the pancreas and salivary glands, which hydrolyzes polysaccharides and is excreted in urine through the glomerulus [19]. Consistent with our findings, Dukkipati et al. reported that elevated IAP can disrupt gastrointestinal motility and reduce perfusion to critical organs such as the lungs and kidneys [20]. For SAP, characteristic manifestations include elevated UAMY levels and multiple organ dysfunction syndrome (MODS). Post-treatment analysis revealed improvements in clinical indicators for both groups, with significantly greater improvement observed in the observation group compared to the control group. These findings suggest that the combined treatment effectively enhances urinary amylase levels and other clinical measurements.

The observation group demonstrated significantly shorter hospital stays, reduced ventilator weaning times, faster improvement of abdominal pain and distension, and quicker pancreatic edema resolution compared to the control group. These findings suggest that CBP combined with antibiotics effectively alleviates symptoms and reduces hospitalization duration.

CC-16, synthesized and secreted by Clara cells in the bronchiolar mucosa, has various biologic functions, including mediating inflammatory responses and respiratory tract injury. Its levels are significantly elevated in lung diseases [21]. SP-D, a collagen glycoprotein, plays a crucial role in maintaining alveolar function and innate lung immunity and is involved in conditions like severe pneumonia and asthma [22]. Research indicates that the severity of ARDS significantly impacts CC-16 and SP-D levels [23]. Post-treatment analysis revealed a significant decrease in CC-16 and SP-D levels in the observation group compared to both pre-treatment levels and the control group. These results suggest that CBP combined with antibiotics effectively reduces these biomarkers, improving lung injury outcomes.

CBP mimics nephron filtration, tubular reabsorption, and excretion functions, introducing arterial blood into a blood filter to enhance lymphatic return and mitigate lung injury caused by inflammatory factors. When combined with antibiotics, CBP further resists bacterial infections, reducing lung infections and

Table 6. Comparison of SP-D and CC-16 levels between the two groups before and after treatment (x ± s)

Group	PaO_2/FiO_2 (mmHg)		PaO_2 (mmHg)		F (times/score)		Plat (cmH_2O)		Peak (cmH_2O)	
	Prior treatment	Post-treatment	Prior treatment	Post-treatment	Prior treatment	Post-treatment	Prior treatment	Post-treatment	Prior treatment	Post-treatment
Control Group (n=64)	147.13±14.74	177.30±13.70#	65.57±6.41	75.12±5.07#	35.26±4.30	26.45±3.95#	26.66±4.45	19.81±3.24#	42.17±4.77	31.55±4.89#
Observation group (n=64)	149.42±12.73	216.71±15.93#	65.69±5.10	84.40±5.17#	34.02±3.58	22.86±3.77#	26.27±3.98	17.75±4.06#	41.35±5.30	27.51±3.80#
t	0.941	15.006	0.117	10.253	1.773	5.260	0.523	3.173	0.920	5.219
P	0.349	<0.001	0.907	<0.001	0.079	<0.001	0.602	0.002	0.359	<0.001

Note: Before comparison treatment, $P<0.05$ was represented by the symbol #. PaO_2/FiO_2: Ratio of partial pressure of arterial oxygen to fractional inspired oxygen, PaO_2: Partial Pressure of Arterial Oxygen, F: Respiratory Rate, Plat: Plateau Pressure, Peak: Peak Inspiratory Pressure.

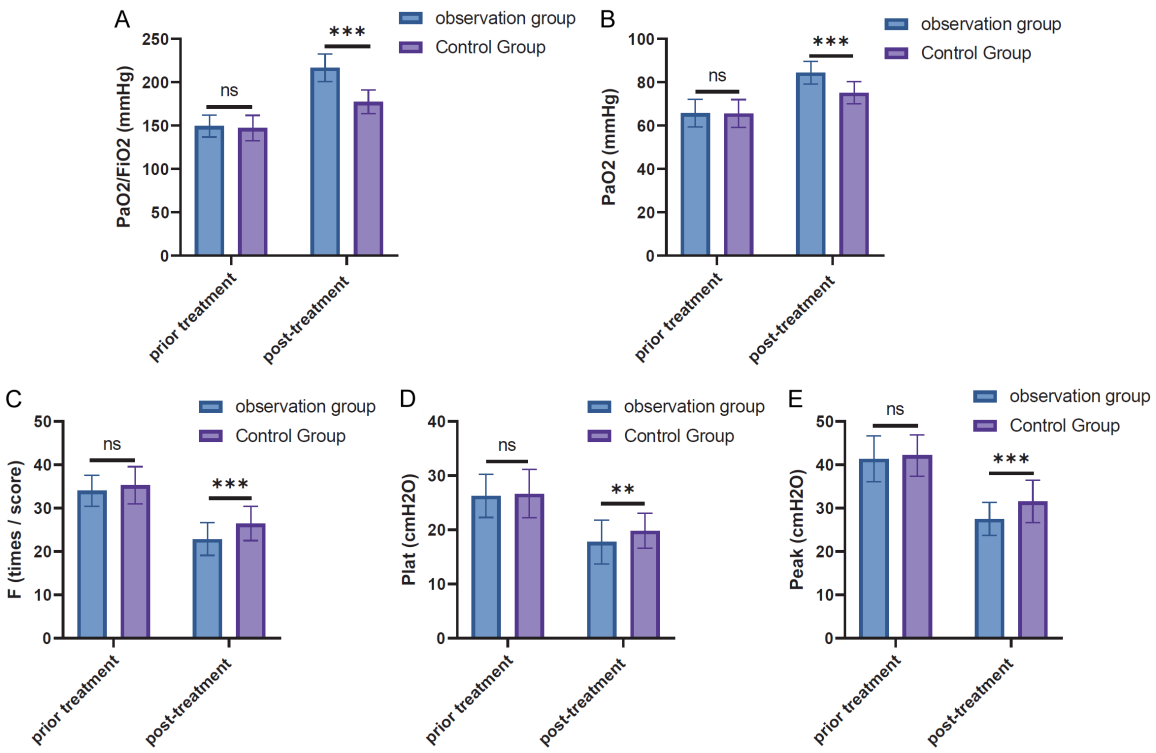

Figure 4. Changes in respiratory mechanics indicators and blood oxygen levels in the two groups. A: PaO_2/FiO_2 (mmHg); B: PaO_2 (mmHg); C: F (times/score); D: Plat (cmH_2O); E: Peak (cmH_2O). PaO_2/FiO_2: Ratio of partial pressure of arterial oxygen to fractional inspired oxygen, PaO_2: Partial Pressure of Arterial Oxygen, F: Respiratory Rate, Plat: Plateau Pressure, Peak: Peak Inspiratory Pressure. ns: No significant difference, **: $P<0.01$, ***: $P<0.001$.

thereby lowering CC-16 and SP-D levels [24, 25].

The development of ARDS in SAP patients is associated with an imbalance of pro-inflammatory and anti-inflammatory mediators. Activated pancreatic enzymes and necrotic pancreatic tissue trigger the rapid release of oxygen free radicals, significantly increasing inflammatory factor levels. TNF-α plays a central role in this process, promoting the release of other inflammatory factors, damaging vascular endothelial cells, and impairing the intestinal mucosal barrier [26]. IL-1β enters the systemic circulation via the portal vein and lymphatic system, exacerbating inflammation [27]. IL-6 stimulates C-reactive protein production, further aggravating the inflammatory response [28].

Post-treatment analysis revealed that the observation group experienced a significant reduction in TNF-α, IL-1β, and IL-6 levels compared to both pre-treatment levels and the control group. These findings indicate that CBP combined with antibiotics effectively reduces systemic inflammation in patients with SAP complicated by ARDS.

CBP's mechanism involves preventing intestinal flora disruption through convection and adsorption of polymer materials, blocking the cytokine-mediated inflammatory cascade, enhancing monocyte antigen presentation, and stabilizing azotemia and fluid-electrolyte balance. When paired with antibiotics, CBP prevents secondary infections, offering dual benefits [28, 29]. These results align with Xu et al., who demonstrated that CBP significantly reduces TNF-α, IL-1β, and IL-6 levels, alleviating systemic inflammation and promoting organ recovery [4]. The combination of CBP with targeted antibiotics further enhances these therapeutic effects by mitigating secondary infections.

The observation group showed significant improvements in PaO_2 and PaO_2/FiO_2 levels compared to the control group. These indicators are critical for evaluating the severity of ARDS and the efficiency of pulmonary gas exchange. Lower levels of PaO_2 and PaO_2/FiO_2

reflect impaired oxygenation and a higher risk of hypoxemia, which exacerbates tissue ischemia and hypoxia, aggravates inflammatory responses, and worsens the patient's condition. The observed improvements suggest that CBP combined with antibiotics effectively enhances oxygenation and reduces hypoxemia risk.

Regarding respiratory mechanics indicators (Peak, Plat, and F), the observation group demonstrated significant improvements compared to the control group ($P<0.05$) in data assessing the mechanical function of the respiratory system and ventilation efficiency. Improved respiratory mechanics lead to enhanced gas exchange, reduced work of breathing, and overall patient recovery.

Studies suggest that lung and intestinal tissues share embryonic homology. In SAP progression, inflammatory factors traverse the intestinal barrier into the bloodstream, invade the lungs through venous reflux and lymphatic circulation, and cause alveolar-capillary injury, impairing oxygen diffusion and leading to ARDS [30, 31]. This cascade results in dyspnea, increased respiratory rates, and critically low levels of PaO_2 and PaO_2/FiO_2. These indicators are essential for monitoring ARDS severity and gas exchange efficiency.

CBP combined with antibiotics can effectively alleviate clinical symptoms, reduce inflammation, and improve patient prognosis, leading to significantly lower mortality rates [32, 33]. This treatment method shortens ventilator weaning time and hospital stays and reduces systemic inflammatory reactions by maintaining internal homeostasis, ensuring nutritional support, and draining excess fluid [34, 35]. Additionally, CBP can remove myocardial inhibitory factors, reduce cardiac preload, and protect cardiopulmonary function [36]. When combined with antibiotics, CBP prevents secondary infections, further improving outcomes [37, 38].

The current findings highlight the therapeutic potential of CBP combined with antibiotics in managing SAP complicated by ARDS. The combination treatment significantly reduces intra-abdominal pressure, amylase levels, and CC-16 and SP-D concentrations, alleviates inflammation, and improves respiratory mechanics and blood gas parameters, ultimately enhancing patient prognosis and reducing mortality.

Despite these promising results, this study has limitations. First, the sample size was relatively small, which may limit the generalizability of the findings. Second, there was no dynamic monitoring of serological indicators. Future research should include larger sample sizes, longer study durations, and multicenter trials to enhance the universality and robustness of the findings [39].

In conclusion, CBP combined with antibiotics shows promise as an effective treatment for SAP patients with ARDS, offering significant advantages over standard of care. Further studies are needed to confirm these findings across diverse clinical settings.

Disclosure of conflict of interest

None.

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