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Original Research Article

Effect of piperacillin sodium and sulbactam sodium on respiratory function in patients with acute respiratory distress syndrome

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Abstract

Purpose: *To investigate the effect of the combination of piperacillin sodium and sulbactam sodium on respiratory function in patients with acute respiratory distress syndrome (ARDS).*
Methods: *The clinical data for 151 ARDS patients admitted in Tianjin Hospital of Nankai Hospital, Tianjin China from January 2020 to January 2021 were analyzed in this retrospective study. The patients were assigned to two groups based on different treatment regimens. Control group (COG) comprised 77 patients who received basic treatment (mechanical ventilation and drug treatment using oxazolidinones), while 74 patients who received basic treatment together with a combination of piperacillin sodium and sulbactam sodium (4 g of piperacillin and 0.5 g of sulbactam (for adults) through intravenous injection for 2 weeks continuously) were in study group (STG). Respiratory function was assessed in the two groups post-treatment using the basic dyspnea index (BDI) measurement. Mechanical ventilation time, intensive care unit (ICU) stay time and 28-day mortality rate after treatment, were also recorded.*
Results: *Following treatment, patients in STG had significantly higher levels of partial pressure of arterial oxygen (PaO_2) and oxygenation index (PaO_2/FiO_2), significantly lower partial pressure of carbon dioxide ($PaCO_2$), markedly lower levels of pentraxin-3 (PTX-3) and procalcitonin (PCT), significantly higher score on BDI scale, and overtly lower mechanical ventilation time and ICU stay time, than COG ($p < 0.05$).*
Conclusion: *Piperacillin sodium and sulbactam sodium combination significantly relieves clinical symptoms of ARDS such as breathlessness and chest discomfort in patients, resulting in improved respiratory function. The effectiveness of this combination makes it a potential first-line treatment for further large-scale investigation in ARDS management.*

Keywords: *Piperacillin sodium, Sulbactam sodium, Acute respiratory distress syndrome (ARDS), Respiratory function*

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute lung disease caused by severe infection, sepsis, shock and trauma, excluding extracardiac factors [1]. The clinical manifestations of ARDS are severe hypoxemia, excessive inflammation and respiratory distress.

It is a non-cardiac disease with high mortality worldwide [2]. Data from epidemiological studies indicate that there are approximately 3 million new cases of ARDS each year in the world, with mortality as high as 46 % [3]. Acute respiratory distress syndrome (ARDS) caused by direct or indirect injuries results in local inflammatory response. Subsequently, inflammatory mediators enter the systemic circulation, thereby causing systemic infection, resulting in an aggravated inflammatory response which eventually becomes uncontrollable and leads to ARDS [4,5]. Although researchers in China and other countries have carried out studies on the treatment of ARDS and made some progress, no specific therapeutic drug has been found at present [6].

The current clinical treatment is mainly based on mechanical ventilation and respiratory support, in combination with active infection control using oxazolidinones, as well as treatment of the primary disease based on pathophysiological characteristics [7]. The common ventilation intervention and drug treatment using oxazolidinones are not very effective in down-regulating systemic inflammation. Therefore, these treatments are not beneficial in alleviating alveolar damage and extra-pulmonary cell function. Piperacillin sodium and sulbactam sodium are broad-spectrum penicillin-based antibiotics [8]. These drugs effectively inhibit the production of beta-lactamase (β-lactamase), with an overt inhibitory effect on multiple pathogenic bacteria.

Compound preparation of piperacillin sodium and sulbactam sodium exerts a strong antibacterial effect on gram-positive and gram-negative bacteria, and it has been widely used in the treatment of respiratory infections and urinary infections. It produces a better curative effect than the antibacterial agents in use. However, there are limited studies on the application of the two drugs for ARDS therapy. Thus, this work investigated the practical impact of piperacillin sodium and sulbactam sodium in clinical treatment of ARDS so as to provide a scientific basis for their clinical application.

METHODS

General data of patients

As a retrospective analysis, this study selected clinical data of 151 ARDS patients treated in Tianjin Hospital of Nankai Hospital for one year. The patients were assigned to COG and STG. The study complied with the guidelines of Declaration of Helsinki [9]. The subjects and their relations were made to understand the aim, significance, and content of the research as well as confidentiality for patients, after which they signed informed consent. This study was approved by the Ethics Committee of Tianjin Hospital of Nankai Hospital (approval no. NKYY-YWKT-IRB-2023-006-01).

Parameters for selection of subjects

Patients who met the clinical diagnostic criteria for ARDS in Modern Respiratory Medicine [10], patients aged more than 18 years old, and patients who had infiltrated shadow in fine mesh type, respiratory distress and refractory hypoxia, were included. However, patients with severe hematological diseases, liver failure, cardiovascular and cerebrovascular diseases, primary tumors, and immune system dysfunction, were excluded.

Treatments

Control group (COG) received basic treatment [11] for ARDS which encompassed the following: firstly, high-flow oxygen was used to improve ventilation function. However, if patients still suffered from dyspnea and if the arterial partial pressure of oxygen was less than 60 mmHg, invasive ventilation treatment assisted by a ventilator was commenced immediately, and respiratory frequency, pressure and oxygen concentration were adjusted according to the clinical situation. Secondly, 600 mg of linezolid and glucose injection (Fresenius Kabi Norge AS; specification: 300 mL; NMPA approval no. HJ20160301) were administered every 12 h continuously through intravenous injection for 10 days. These were aimed at effectively controlling inflammatory responses in patients. Then, patients were maintained on a negative fluid balance during the acute phase, and diuretics were used if patients' albumin values were less than 35 g/L. After injecting 100 mL of 0.9 % sodium chloride solution (NMPA approval no. H43020456; manufacturer: Hunan Kelun Pharmaceutical Co. Ltd.; batch no. KL0A0264) at a dose of 100 mL, a solution of human serum albumin (Takeda Manufacturing Italia S.P.A. specification: 20 %, 50 mL; NMPA (I): S20180020) was given as supplement continuously for 1 week at a dose of 50 mL through intravenous infusion in line with the principle of less amount with multiple injections, with injection rate varying from fast to slow.

Finally, enteral nutritional support was established using a nasogastric tube through which enteral nutrition solution was intermittently administered.

Patients in study group (STG) received the same basic treatment described above for control group, in addition to piperacillin sodium and sulbactam sodium (Shandong Anxin pharmaceutical Co. Ltd; specification: 4.5 g; NMPA approval no. H20123402) at the adult dose of 1.5 g (1 g of piperacillin and 0.5 g of sulbactam) or 3.0 g (2.0 g of piperacillin and 1.0 g of sulbactam), with maximal total dose of 12.0 g (8.0 g of piperacillin and 4.0 g of sulbactam) and maximal sulbactam dose of 4.0 g every day. In addition, 100 mL of 0.9 % sodium chloride was added *via* intravenous drip for 20 - 30 min. The treatment was given every 8 h, with continuous intravenous infusion for 2 weeks.

Patients in both groups were monitored for a period of 28 days for signs of toxicity and mortality.

Evaluation of parameters/indices

Blood gas analysis

Arterial blood samples (2-mL portions) were collected before and 7 days after treatment in special syringes, and a Jisheng (Shanghai) model GEM 5000 blood gas analyzer was used to measure PaO_2, $PaCO_2$ and PaO_2/FiO_2.

Serum indices

Enzyme-linked immunosorbent assay was used for assay of pentraxin-3 (PTX-3) and procalcitonin (PCT). Post-therapy, 3 mL of fasted venous blood was subjected to 10-min centrifugation at 3000 rpm, and the serum obtained was subjected to determination of levels of PTX-3 and PCT using assay kits provided by Shanghai Enzyme-linked Biotechnology Co. Ltd.

Scores on respiratory function

The basic dyspnea index (BDI) scale [12] was applied for assessment of respiratory function. The scale assessed three dimensions *viz*: functional impairment, degree of dyspnea, and level of effort put in to complete activities, with a 5-level scoring standard. The score range for each dimension was 0-4 points, while the overall score varied from 0 to 12 points. The lower the score, the higher degree of dyspnea in patients.

Clinical indicators

The mechanical ventilation time, ICU stay time, and 28-day mortality after treatment were recorded.

Statistical analysis

In this study, the SPSS 26.0 software was used for statistical analysis, while Figures were drawn using GraphPad Prism 7 software. Enumeration results are expressed as n (%), and were compared using χ^2 test, while measurement data that met normal distribution are presented as mean ± standard deviation (SD), and were compared using *t*-test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Clinical profile of patients

As presented in Table 1, the data of patients in the 2 groups were comparable.

Table 1: Comparison of clinical data of subjects in the 2 groups

Parameter	COG (n=77)	STG (n=74)	χ^2/t	*P*-value
Gender			0.001	0.977
Male	47 (61.04)	45 (60.81)		
Female	30 (38.96)	29 (39.19)		
Average age (years)	38.78±12.18	38.51±12.74	0.781	0.437
BMI (kg/m^2)	23.62±2.92	24.27±2.91	1.333	0.187
Duration of disease (days)	5.82±2.08	5.80±1.92	0.048	0.962
Primary diseases			0.101	0.992
Sepsis	19 (24.68)	18 (24.32)		
Pneumonia	21 (27.27)	21 (28.38)		
Thoracic trauma	16 (20.78)	14 (18.92)		
Shock	21 (27.27)	21 (28.38)		
Educational level			0.320	0.988
College and above	20 (25.97)	19 (25.68)		
Senior high school	16 (20.78)	18 (24.32)		
Junior high school	26 (33.77)	23 (31.08)		
Primary school	10 (12.99)	9 (12.16)		
Illiterate	5 (6.49)	5 (6.76)		

Values are presented as n (%) and as mean ± SD. BMI: Body mass index

Blood gas values

After treatment, STG had significantly higher PaO_2 and PaO_2/FiO_2, and lower $PaCO_2$ than the COG ($p < 0.05$; Table 2).

Serum indices

After 7 days of treatment, patients in STG had significantly lower levels of PTX-3 and PCT than those in COG ($p < 0.05$), as presented in Figure 1. The average PTX-3 values in the COG and STG after treatment were 1.12 ± 0.14 µg/mL and 1.03 ± 0.13 µg/mL, respectively. There was a significant difference in PTX-3 levels of patients in both groups ($t = 3.933$, $p < 0.001$). Moreover, the PCT levels of patients in both groups differed significantly, with the average PCT levels in COG and STG after treatment being 0.51 ± 0.07 µg/L and 0.37 ± 0.08 µg/L, respectively ($t = 11.779$, $p < 0.001$).

Scores on respiratory function

After 7 days of treatment, the BDI score in STG was markedly higher than that in COG ($p < 0.05$; Table 3).

Clinical indicators

The STG had significantly lower mechanical ventilation time and ICU stay time when compared to the COG. However, 28-day mortality was similar in the 2 groups (Table 4).

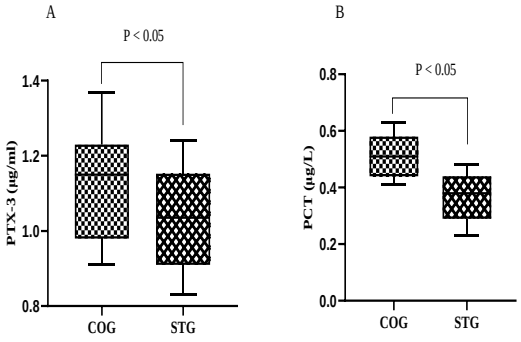

Figure 1: Comparison of serum indices in both groups (mean ± SD). A and B show the comparison of post-treatment levels of serum PTX-3 and PCT, respectively between the 2 groups after treatment. PTX-3: pentraxin-3; PCT: procalcitonin

DISCUSSION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by alveolar capillary injury due to aggravated infection, trauma, shock and other intrapulmonary and extrapulmonary events, and it is a serious form of acute lung injury [12].

Table 2: Values of blood gas parameters in both groups (Mean ± SD)

Index	Group	COG (n=77)	STG (n=74)	*t*	*P*-value
PaO_2 (mmHg)	Prior to therapy	50.09±3.15	50.94±3.62	1.359	0.178
	After therapy	67.58±3.96	82.48±4.85*	21.958	<0.001
PaO_2/FiO_2	Prior to therapy	166.24±4.03	166.95±3.78	1.154	0.252
	After therapy	280.12±7.94	305.15±9.19*	16.530	<0.001
$PaCO_2$ (mmHg)	Before treatment	55.65±3.33	55.60±3.27	0.219	0.827
	After treatment	42.54±2.98	39.77±2.06*	6.828	<0.001

*$P < 0.05$, vs COG after 7 treatment days

Table 3: Scores of BDI in both groups (mean ± SD, points)

Group	COG (n=77)	STG (n=74)	t /χ^2	*P*-value
Functional impairment	2.03±1.04	2.95±1.06*	5.741	<0.001
Degree of dyspnea	2.17±1.37	3.12±1.01*	4.812	<0.001
Effort levels to complete activities	1.61±1.26	2.82±1.15*	6.927	<0.001
Total score	5.82±1.96	8.89±1.90*	10.499	<0.001

*$P < 0.001$, vs. COG after 7 treatment days. BDI: basic dyspnea index

Table 4: Levels of clinical indicators in both groups (mean ± SD)

Group	COG (n=77)	STG (n=74)	*t* /χ^2	*P*-value
Mechanical ventilation time (days)	9.12±1.88	7.28±1.94*	5.842	<0.001
ICU stay time (days)	11.53±2.26	9.16±2.08*	6.309	<0.001
28-day mortality (%)	6 (3.3)	4 (20.0)	0.348	0.555

*$P < 0.001$, vs. COG after 7 treatment days

The clinical features of ARDS are decreased lung volume, reduced lung compliance, progressive hypoxemia, and disordered blood flow system. In X-ray films, ARDS shows diffuse alveolar infiltration. The pathogenesis of ARDS is complex, and the specific mechanism involved is indistinct [13]. However, researchers have associated ARDS with a variety of factors such as imbalance in inflammatory response, coagulation dysfunction, alveolar-capillary barrier dysfunction, oxidative stress and apoptosis. Based on its pathological mechanism, the clinical treatment methods presently used are mainly mechanical ventilation, anti-infectives and symptomatic intervention against the primary disease. Although the present treatment modalities have certain clinical benefits, the reductions in clinical symptoms of ARDS are not satisfactory, and the treatments are marred with high mortality in ARDS patients.

In clinical investigations, it was found that the pathogenesis of ARDS is intimately associated with impairment of immune homeostasis in the pulmonary microenvironment [14]. Commensal bacteria and multiple cell populations are involved in regulating immune homeostasis in the pulmonary microenvironment which is one of the organized environments in direct contact with the external environment. In general, the pulmonary microenvironment is in a state of immune tolerance, and cell populations related to lung immunity such as type II alveolar epithelial cells, alveolar macrophages and regulatory T cells jointly maintain immune balance in the lungs.

However, following the onset of ARDS, respiratory storms result due to impaired immune homeostasis in the lungs, neutrophil infiltration, and reactive oxygen species [15]. Macrophages, dendritic cells, and recruited monocytes release a large number of pro-inflammatory cytokines, leading to cytokine storms [16]. This situation simultaneously deteriorates pulmonary immune environment, resulting in impaired alveolus and other tissue functions, thereby affecting the patient's lung ventilation status. Therefore, the use of antibiotics to regulate pulmonary inflammatory response is expected to improve the pulmonary ventilation status of patients.

Piperacillin and sulbactam constitute an antibiotic combination composed of a 4:1 ratio of the two drugs. Piperacillin sodium, a penicillin antibiotic, has a strong inhibitory effect on gram negative bacteria [17]. Sulbactam sodium has a broad-spectrum and strong inhibitory effect on beta-lactamase (β-lactamase) [18]. The combination of both drugs produces a good synergistic antibacterial effect which is clinically applied for treating various infectious diseases. This work has demonstrated that following treatment, study group (STG) had significantly lower levels of PTX-3 and PCT, and markedly better levels of blood gas indices than control group (COG), indicating that the addition of the two drugs to the basic therapeutic protocol has the potential to drastically reduce inflammation-related response and ventilation status of patients.

The reason for this claim is that piperacillin sodium has a strong capacity to penetrate the cell walls of bacteria, and it causes bacteria to rapidly become spheroids, thereby making them substrates for rupture and dissolution while inhibiting cell wall synthesis. Thus, it exerts a strong and rapid bactericidal effect on a variety of bacteria [19].

Sulbactam, a semi-synthetic β-lactamase inhibitor, effectively makes up for the shortcomings of piperacillin sodium which is not resistant to β-lactamase, and it exerts an irreversible inhibitory effect on β-lactamase produced by *S. aureus* and most gram -ve organisms [20]. The combination of the two produces a significant clinical antibacterial effect. Thus, the clinical outcomes in STG subjects were superior to those in COG in terms of mechanical ventilation time and ICU stay time, although there was no significant difference in 28-day mortality between the two groups.

Limitations of the study

There are some shortcomings in this study. For example, the specific mechanism involved in multi-target signaling pathway of the two antibiotics for ARDS therapy is still unclear. At the same time, no research was done on tolerance and adverse reactions of patients, and only a few quantitative indicators were assessed.

CONCLUSION

The application of sulbactam and piperacillin in ARDS therapy improves pulmonary ventilation status and respiratory function of subjects, as well as shortens hospitalization time. The parameters assessed should be expanded to further clarify the target signaling pathway in order to provide a more objective and comprehensive basis for the clinical treatment of ARDS in the future.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We 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 the authors. Yan Li and Jie Cao conceived and designed the study, and drafted the manuscript. Suhang Wang and Jing Zhang collected, analyzed and interpreted the experimental data. Yan Li and Jie Cao revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee of Tianjin Hospital of Nankai Hospital (approval no. NKYY-YWKT-IRB-2023-006-01).

Availability of Data and Materials

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

***Use of Artificial Intelligence*/Large Language Models**

None provided.

Use of Research Reporting Tools

None provided.

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