

Original Article

Effect of cefoperazone sulbactam sodium combined with meropenem on the immune function in the treatment of neonatal pneumonia caused by multidrug-resistant bacteria

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Abstract: Objective: To explore the effect of cefoperazone sulbactam sodium combined with meropenem on the immune function in the treatment of neonatal multi-drug resistant pneumonia. Methods: Altogether 130 children with pneumonia caused by multi-drug resistant bacteria admitted to our hospital from January 2016 to January 2019 were recruited as the study cohort. The children were randomly divided into a combined group (n=80, combined therapy) and a control group (n=50, cefoperazone sulbactam sodium therapy). Their clinical indexes and their pulmonary function indexes, their serum heparin-binding protein (HBP) 1,25-dihydroxy vitamin D3 [1,25-(OH)2D3] levels, and their inflammatory factors and immune indexes were observed. The bacterial eradication rates, total effective rates, and adverse reaction rates of the two groups were investigated. Results: Compared with the control group, the cough disappearance times, the antipyretic times, the pulmonary rales disappearance times, and the hospital stay lengths in the combination group were shorter, the FEV1% Pred (the percentage of forced expiratory volume in one second compared to the predicted value) and the FEV1/Fvc% (the percentage of forced expiratory volume in one second compared to the forced vital capacity) were higher, the HBP levels and the inflammatory factor CRP and IL-6 levels were lower, the 1,25-(OH)2D3, and the immune index gA, IgG, and C4 levels were higher, and the bacterial eradication rates and the total effective rates were higher, and the incidence of adverse reactions was lower. Conclusion: Cefoperazone sulbactam sodium combined with meropenem can improve the immune function of newborn children with multi-drug resistant pneumonia.

Keywords: Cefoperazone, sulbactam sodium, meropenem, multidrug-resistant bacteria, pneumonia

Introduction

Pneumonia is a common disease. About 400-500 million people are infected every year [1, 2], which causes an extremely high mortality. Meanwhile, bacterial pneumonia accounts for the majority [3, 4] of cases. Many drug-resistant bacteria can also cause multidrug-resistant gram-negative organisms, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, which are usually associated with nosocomial pneumonia in intensive care units (ICU). These organisms easily cause an increase in the incidence and mortality of infectious pneumonia [5-7]. Some

drug-resistant bacteria, such as *Klebsiella*, exist in neonatal hospitals and can cause pneumonia. Pneumonia caused by these drug-resistant bacteria is a great threat to newborns, which is one of the reasons for the increase of neonatal mortality [8, 9]. Therefore, in order to protect newborns, it is necessary to find a treatment for multiple infectious pneumonia. In this study, we will explore the effects of cefoperazone, sulbactam sodium, and meropenem.

Cefoperazone sulbactam sodium is the third generation of cephalosporin, which is a broad-spectrum β -lactam/ β -lactamase inhibitor. It has many clinical uses, and it has a good effect

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on various infections and inflammation caused by infections [10-12], and it also has an effect on pneumonia caused by multi-drug resistant bacteria infections in hospitals [13]. And the other drug, meropenem, is a carbapenem anti-bacterial agent, which has effects on many kinds of bacteria, such as gram-negative and gram-positive bacteria (including *Penicillium* and cephalosporinase). The principle is to play a bactericidal role by combining it with a penicillin-binding protein in the bacterial cell wall and inhibiting the cross-linking of peptidoglycan related to cell wall synthesis, thus leading to cell death [14-16]. There are few related studies on the combined treatment of these drugs for pneumonia caused by multidrug-resistant bacteria in newborns, so this study intended to analyze the combination of these drugs in the neonatal infection of multidrug-resistant bacteria pneumonia by examining the immune function, inflammatory factor levels, lung function recovery, and other indicators.

Methods

General data

Altogether 130 children with pneumonia caused by multi-drug resistant bacteria admitted to Hainan General Hospital from January 2016 to January 2019 were recruited as the study cohort. The children were randomly divided into a combined group and a control group. There were 80 children in the combined group, including 44 males and 36 females. The average age was (13.01 ± 6.03) days, the average weight was (3.62 ± 0.24) kg, and the average course of disease was (2.97 ± 1.85) days. There were 50 children in the control group, including 27 males and 23 females. The average age was (12.89 ± 6.34) days, the average weight was (3.57 ± 0.32) kg, and the average course of disease was (3.09 ± 1.62) days. The family members signed a consent form, and the study was approved by the Ethics Committee.

Inclusion criteria: all these children were diagnosed with neonatal infectious pneumonia in our hospital, and after their chest X-rays, it was found that their lung texture was disordered and increased. The children were less than 30 days old and had clinical manifestations such as high fever, cyanosis, cough and lung rales. The children were treated for the first time. Exclusion criteria: children with con-

genital heart disease, congenital lung dysplasia, or central nervous system diseases, and children who were allergic to cefoperazone sulbactam sodium and meropenem.

Methods

Both groups of children were given the basic treatment, including oxygen inhalation, nutritional support, cough relief, rehydration, and maintenance of their water and electrolyte balance. The control group was treated with cefoperazone sulbactam sodium. Cefoperazone sulbactam sodium (Qilu Pharmaceutical, SFDA approval no.: J20140169) was used for an intermittent intravenous drip, with 40-80 mg/kg.d drugs dissolved in 5% glucose solution or 100 ml of 0.9% sodium chloride, and with an interval of 30-60 minutes, twice a day for a total of 7 days. The children in the combined group were treated with cefoperazone sulbactam sodium and meropenem, and the administration of the cefoperazone sulbactam sodium was the same as it was in the control group. The use of meropenem (Dainippon Sumitomo Pharma (Suzhou) Co., Ltd., SFDA approval no.: H20093264) was as follows: 20~30 mg/kg meropenem was added to 10 mL saline for an intravenous injection once a day for 7 days.

Indicators

(1) Clinical indicators: The related clinical indexes of the two groups were investigated and compared, including the cough disappearance times, the antipyretic times, the pulmonary rales disappearance times, and the lengths of the hospital stays.

(2) Lung function: The lung function of the two groups of children before the treatment and 14 days after treatment was measured. The indexes included FEV1% Pred (the percentage of forced expiratory volume in one second compared to the predicted value) and FEV1/Fvc% (the percentage of forced expiratory volume in one second compared to the forced vital capacity). Masterscreen (JAEGER, Germany) was used to determine the values.

(3) Serum levels: Before treatment and at 14 days after the treatment, 5 ml blood was collected from the patients in both groups and put in non-anticoagulation sterile test tubes, and

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then centrifuged at $1500 \times g$ at 4°C for 10 min. The serum was placed in a freezer at -70°C prior to determining the various serum levels.

The heparin-binding protein (HBP) and 1,25-dihydroxyvitamin D3 (1,25-(OH)₂D₃) expression levels were measured using ELISA before and after the treatment.

Quantification of the inflammatory factors: Before and after treatment, the serum C-reactive protein (CRP) and serum interleukin-6 (IL-6) levels were measured and compared.

Immunological indicators: Before and after the treatment, the IgM, IgA, IgG, and complement C3, C4 levels of the two groups were measured and compared.

(4) **Bacterial eradication:** Blood was collected from the children in the two groups after the treatment and cultured. At the same time, the children's sputum was collected for sputum culture examinations. Before and after the treatment, a bacteriological examination was carried out on the cultured samples, and the bacterial eradication of the children was investigated. If the bacteriological examination results were negative after the treatment, the children who were re-infected by the same pathogenic bacteria were counted as the number of re-infected cases. If the pathogen was not detected in the two consecutive bacteriological examinations after the treatment, but there were other pathogenic bacteria growth, it was counted as the number of replacement cases. If the bacteriological examinations were positive two consecutive times after the treatment, it was counted as the number of replacement cases. If the bacteriological examinations were negative two consecutive times after the treatment, it was counted as the number of eradication cases. After that, the bacterial eradication rates of the two groups of patients were calculated (bacterial eradication rate = (number of eradication cases + number of replacement cases)/total number of cases \times 100%).

(5) **Total effective rate:** The total effective rates of the two groups were investigated and compared. The criteria are as follows: after the treatment, the vital signs such as respiration, heart rate, and body temperature of the patient returned to normal, the lung imaging examination results showed normal, the white blood cell count was normal, and the sputum culture

results showed negative, which indicated cured; after the treatment, the patient's vital signs such as respiration, heart rate and body temperature returned to normal, the results of the lung imaging examination were significantly improved, the white blood cell count tended to normal, and the sputum culture results showed positive or negative, which indicated significantly improved; after the treatment, the patient's vital signs such as respiration, heart rate, and body temperature were significantly improved, the lung imaging examination results were improved, the white blood cell count was improved, and the sputum culture results showed positive, which indicated effective; after the treatment, the vital signs such as respiration, heart rate, and body temperature were not improved, the lung imaging examination was unchanged, the white blood cell count was increased, and the sputum culture result showed positive, which indicated ineffective. Total effective rate = basically cure rate + markedly effective rate + effective rate.

(6) **Adverse reactions:** All types of adverse reactions in the two groups were counted. The related indexes were renal function injuries, rash, nausea, and vomiting, hemoglobin decrease, and secondary fungal infections.

Statistical methods

SPSS 19.0 (Asia Analytics Formerly SPSS, China) was used for the data analysis. χ^2 tests were used for the count data. The measurement data were represented as $X \pm S$ and analyzed using t tests. When $P < 0.05$, a difference was considered to be statistically significant.

Results

General data

There were no significant differences between the two groups in their general clinical data such as sex, average age, average course of the disease, or average weight ($P > 0.05$), see **Table 1** for details.

The clinical indicators of the children in the combined group were better than in the control group

The cough disappearance times, the antipyretic times, the pulmonary rales disappearance times, and the hospital stay lengths were com-

Table 1. The general clinical data of the children in two groups

Group	Combined (n=80)	Control group (n=50)	t/X ²	p
Gender			0.01	0.911
Male	44 (55.00)	27 (54.00)		
Female	36 (45.00)	23 (46.00)		
Average age (d)	13.01±6.03	12.89±6.34	0.11	0.914
Average course of disease	2.97±1.85	3.09±1.62	0.38	0.707
Average weight (Kg)	3.62±0.24	3.57±0.32	1.01	0.312
Childbirth			0.40	0.818
Natural birth	38 (47.50)	24 (48.00)		
Cesarean section	32 (40.00)	18 (36.00)		
Fast labor	10 (12.50)	8 (16.00)		
Residence of children			0.24	0.623
Rural	24 (30.00)	13 (26.00)		
Urban	56 (70.00)	37 (74.00)		
Family type of children			0.48	0.487
Other	8 (10.00)	7 (14.00)		
Core family	72 (90.00)	43 (86.00)		

(2) The CRP and IL-6 levels in the combined group were lower than they were in the observation group after the treatment.

The CRP and IL-6 levels were compared between the two groups. The CRP and IL-6 levels in the combined group were lower than they were in the observation group (P<0.05). See **Figure 4** for details.

(3) The children's immunological indexes in the combined group were higher than they were in the observation group.

The immunological indexes of the two groups were compared. After the treatment, the immunoglobulin IgA, IgG and

pared between the two groups, and the times in the combined group were all shorter than they were in the control group (P<0.05). See **Figure 1** for details.

The recovery of the pulmonary function indexes of the children in the combined group was better than the recovery of the children in the control group

FEV1% Pred and FEV1/Fvc% were compared between the two groups. The lung function of both groups recovered after the treatment, and the FEV1% Pred and the FEV1/Fvc% in the combined group were higher than they were in the control group (P<0.05). See **Figure 2** for details.

Comparison of serum test results

(1) After the treatment, the HBP levels in the combined group were lower than they were in the observation group, and the 1,25-(OH)2D3 levels were higher than they were in the control group.

The HBP and 1,25-(OH)2D3 levels were compared between the two groups. After the treatment, the HBP levels in the combined group were lower than they were in the observation group and the 1,25-(OH)2D3 levels were higher than they were in the control group (P<0.05). See **Figure 3** for details.

complement C4 levels in the two groups changed significantly, and the IgA, IgG, and C4 levels in the combined group were higher than they were in the control group (P<0.05). See **Figure 5**.

The bacterial eradication rate of the children in the combined group was higher than it was in the control group

After investigating the two groups' bacterial eradication rates, it was found that the bacterial eradication rate of the combined group was significantly higher than it was in the control group (P<0.05). See **Table 2** for details.

The total effective rate of the children in the combined group was higher than it was in the control group

After investigating the two groups' total effective rates, it was found that the total effective rate in the combined group was significantly higher than it was in the control group (P<0.05). See **Table 3** for details.

The incidence of adverse reactions in the combined group was higher than it was in the control group

After investigating the incidence of adverse reactions in the two groups, it was found that

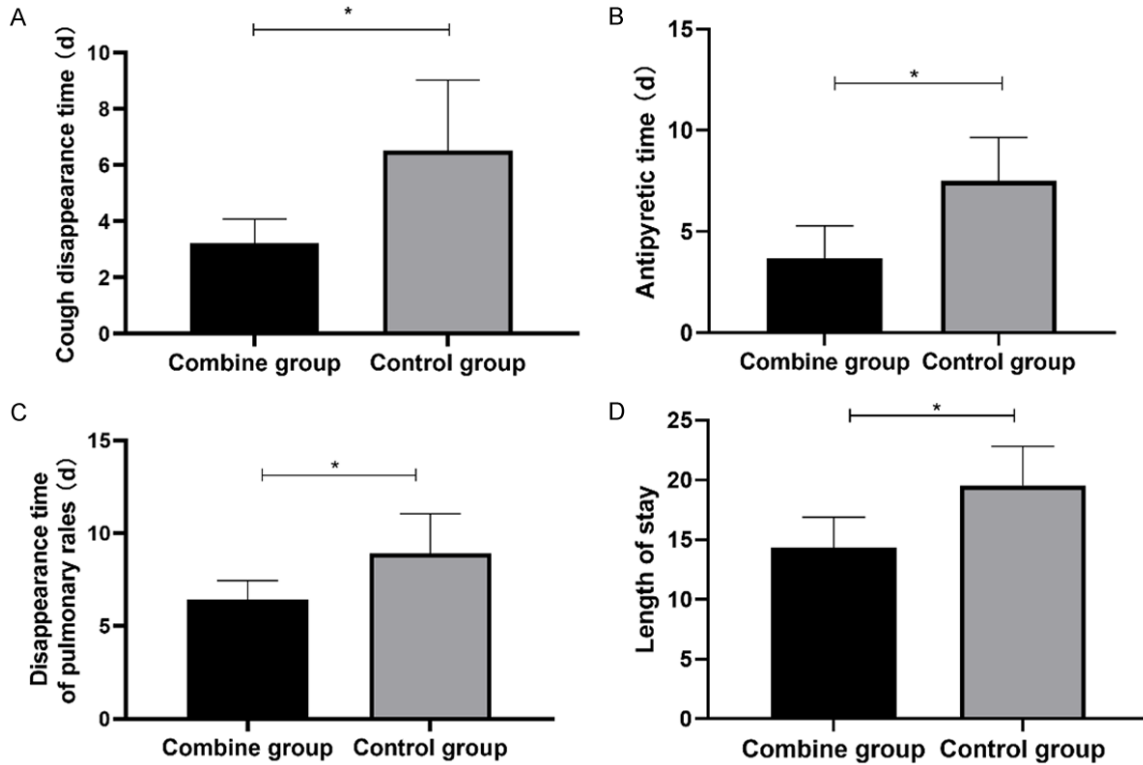


Figure 1. The clinical indicators of the children in the two groups: (A) The cough disappearance times in the combined group were shorter than they were in the control group ($P < 0.05$); (B) The antipyretic times in the combined group were shorter than they were in the control group ($P < 0.05$); (C) The disappearance times of the pulmonary rales in the combined group were shorter than they were in the control group ($P < 0.05$); (D) The length of hospital stays in the combined group were shorter than they were in the control group ($P < 0.05$). Note: * means compared with the control group, $P < 0.05$.

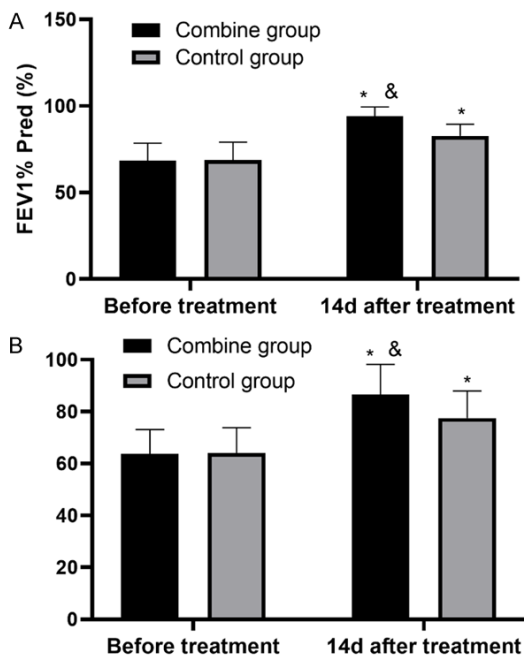


Figure 2. The pulmonary function indexes of the children in the two groups: (A) FEV1% Pred: Both groups

recovered after the treatment, and the FEV1% Pred levels in the combined group were higher than they were in the control group ($P < 0.05$); (B) FEV1/Fvc%: Both groups recovered after the treatment, and the FEV1/Fvc% in the combined group was higher than it was in the control group ($P < 0.05$). Note: * means compared with before the treatment, $P < 0.05$; & means compared with the control group, $P < 0.05$.

the incidence of adverse reactions in the combined group was significantly higher than it was in the control group ($P < 0.05$). See **Table 4** for details.

Discussion

After the lungs are infected by pathogens such as bacteria, inflammation occurs, which is a normal and natural reaction produced by the immune system. If the inflammatory reaction is not stopped quickly, it will lead to pneumonia [17, 18]. To treat bacterial pneumonia, it is necessary to eliminate the excessive inflammation and to restore the steady state of lung tissue

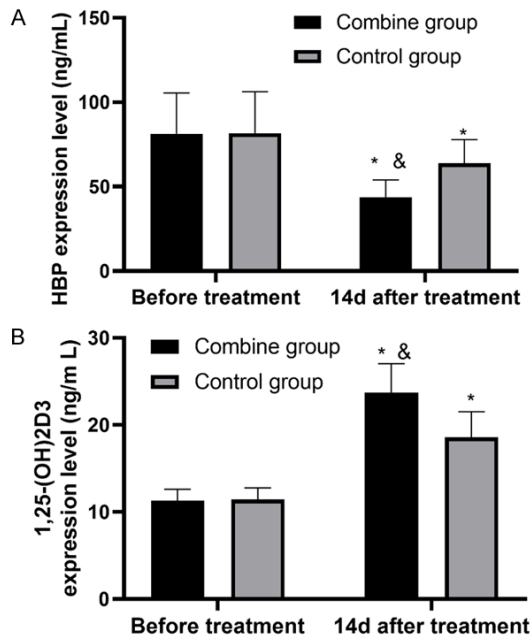


Figure 3. The HBP and 1,25-(OH)2D3 levels in the two groups of children: (A) HBP: Both groups' levels were decreased after the treatment, and the HBP levels in the combined group were lower than they were in the control group ($P < 0.05$); (B) 1,25-(OH)2D3: The 1,25-(OH)2D3 levels in the combined group were higher than they were in the control group ($P < 0.05$). Note: * means compared with before the treatment, $P < 0.05$; & means compared with the control group, $P < 0.05$.

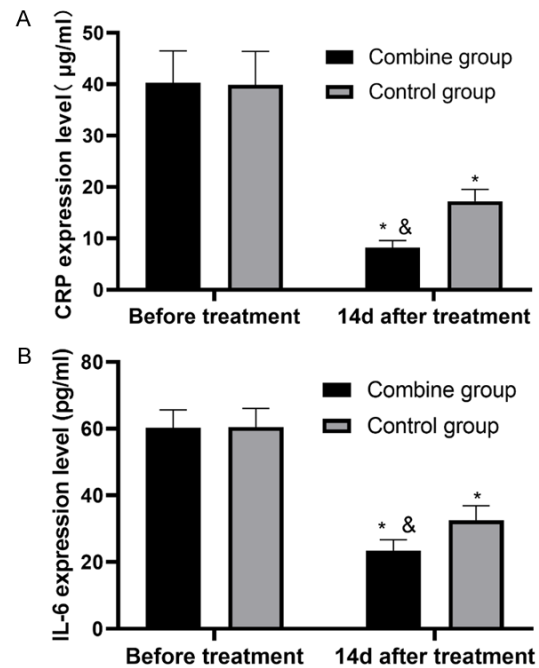


Figure 4. The inflammatory factor expression levels in the two groups: (A) CRP: After the treatment, the CRP level in the combined group was lower than it was in the control group ($P < 0.05$); (B) IL-6: The IL-6 levels in the combined group were lower than they were in the control group ($P < 0.05$). Note: * means compared with before the treatment, $P < 0.05$; & means compared with the control group, $P < 0.05$.

[19-21]. At the same time, it is also very important to eliminate bacteria, especially drug-resistant bacteria [22]. In this study, we analyzed the effect of cefoperazone sulbactam sodium combined with meropenem on multidrug-resistant bacteria. We will discuss our results from the perspectives of bacterial immunity and inflammation.

In terms of bacterial immunity, the eradication rate of cefoperazone sulbactam sodium combined with meropenem was significantly higher than it was with the monotherapy in the control group, and most immunological indexes were also higher than they were in the control group. Multi-drug-resistant bacteria are widely distributed in nature and can survive on wet and dry surfaces, so it is of great significance to control the infections of these drug-resistant bacteria [23, 24]. Cefoperazone has bactericidal effects, and as a β -lactam antibiotic, it needs to be used together with a β -lactamase inhibitor such as sulbactam sodium. This can

make the inactivation process of most β -lactamases produced by multi-drug resistant bacteria irreversible, thus enhancing the activity of cefoperazone [25]. Studies have shown that cefoperazone sulbactam sodium has a good antibacterial effect on multi-drug resistant bacteria infections [26]. Meropenem, a carbapenem antibacterial agent, has a stable hydrolysis effect on β -lactamase. Meropenem exerts its bactericidal effect by combining with penicillin-binding protein (PBP) in bacterial cell walls and inhibiting the cross-linking of peptidoglycans related to cell wall synthesis, thus leading to cell death [27]. The combination of the two drugs has a better effect on the elimination of drug-resistant bacteria. Because of the special structure on the surface of these bacteria, they can disable the signal of the host's immune system and escape from the immune response. If the content of multi-drug-resistant bacteria is too high, it can easily and seriously damage patients' immune systems [28]. Combined with the results of this experiment, after the combined treatment of

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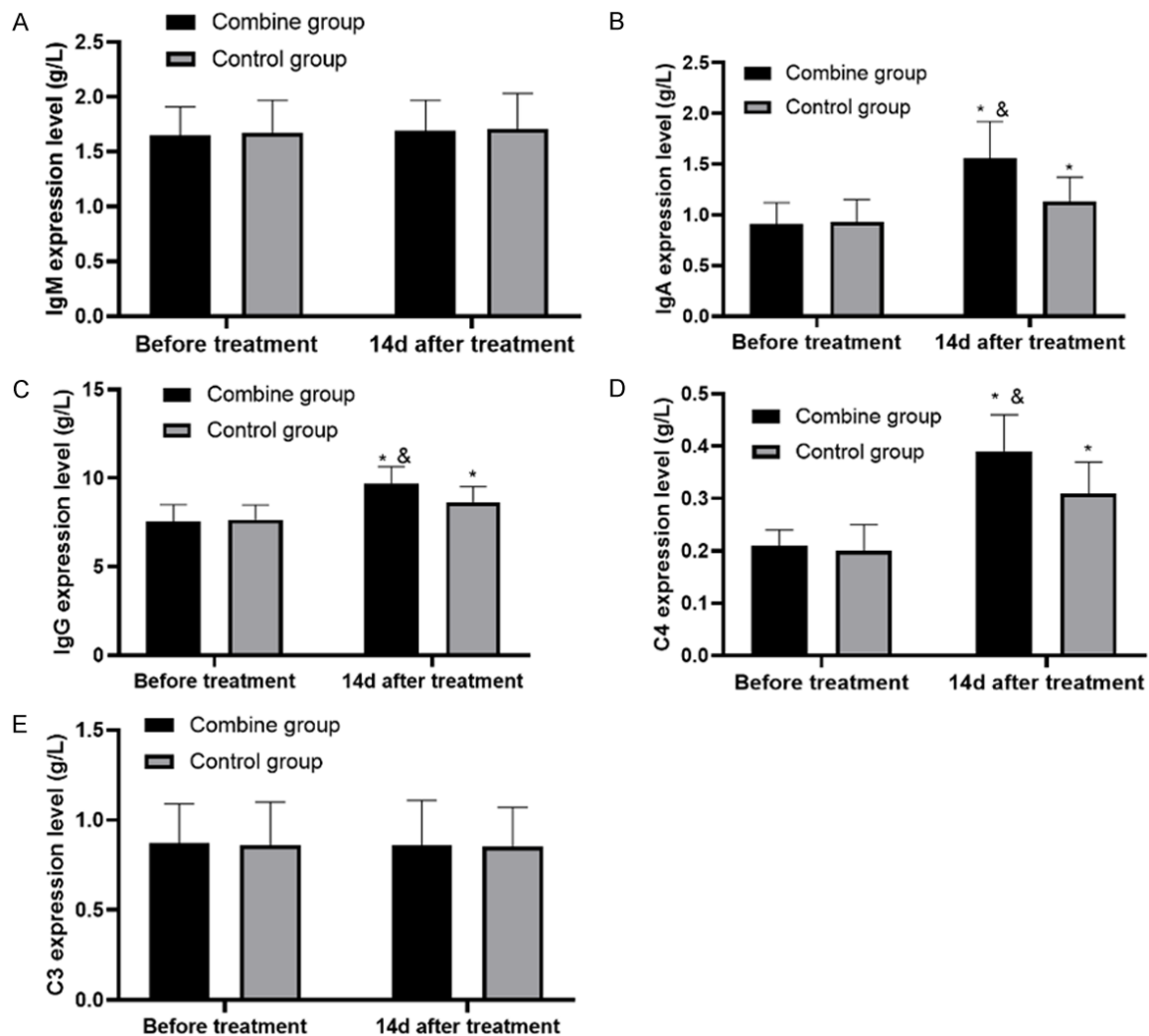


Figure 5. The immune indicators of the children in the two groups: (A) IgM: There was no difference between the two groups before and after the treatment ($P>0.05$); (B) IgA: There was no difference between the two groups before the treatment, and the IgA level in the combined group was higher than it was in the control group after the treatment ($P<0.05$); (C) IgG: There was no difference between the two groups before the treatment, and the IgG level in the combined group was higher than it was in the control group after the treatment ($P<0.05$); (D) C4: There was no difference between the two groups before the treatment, but the C4 level in the combined group was higher than it was in the control group after the treatment ($P<0.05$); (E) C3: There was no difference between the two groups before and after treatment ($P>0.05$). Note: * means compared with before the treatment, $P<0.05$; & means compared with the control group, $P<0.05$.

Table 2. The total effective rates of the two groups of patients

Classification	Combined group (n=80)	Control group (n=50)	χ^2	P
Number of reinfection cases	3 (3.75)	7 (14.00)	-	-
Number of uncleared cases	1 (1.25)	6 (12.00)	-	-
Number of replacement cases	20 (25.00)	18 (36.00)	-	-
Number of eradication cases	56 (70.00)	19 (38.00)	-	-
Eradication rate (%)	76 (95.00)	37 (74.00)	11.94	>0.001

effectively eliminated, and their immune systems recovered better. From this point of view, the combined treatment of cefoperazone sulbactam sodium and meropenem can effectively clean up bacteria to restore the function of the immune system.

cefoperazone sulbactam sodium and meropenem, these bacteria in children's bodies were

In terms of inflammation, HBP was lower, 1,25-(OH)₂D₃ was higher, and the inflammatory fac-

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Table 3. The total effective rates of the two groups of patients

Classification	Combined group (n=80)	Control group (n=50)	χ^2	P
Cured	44 (55.00)	16 (32.00)	-	-
Markedly effective	20 (25.00)	14 (28.00)	-	-
Effective	14 (17.50)	11 (22.00)	-	-
Ineffective	2 (2.50)	9 (18.00)	-	-
Total effective rate (%)	78 (97.50)	41 (82.00)	9.24	0.002

Table 4. The incidences of complications in the two groups

Classification	Combined group (n=80)	Control group (n=50)	χ^2	P
Renal function injury	0 (0.00)	1 (2.00)	-	-
Rash	1 (1.25)	3 (6.00)	-	-
Nausea and vomiting	1 (1.25)	3 (6.00)	-	-
Hemoglobin drops	2 (2.50)	2 (4.00)	-	-
Secondary fungal infection	0 (0.00)	1 (2.00)	-	-
Incidence of complications (%)	4 (5.00)	10 (20.00)	7.20	0.007

tors CRP and IL-6 were higher in the combined group after the treatment. When patients are infected with bacterial pneumonia, the bacteria invading the respiratory system will release the cytotoxic products of pneumonia and kill respiratory cells. With the increase of bacterial resistance to drugs, it is easy to cause further damage to the immune system and a further deterioration of inflammation [1, 29, 30]. HBP (heparin binding protein) is a newly discovered inflammation biomarker. In a pathogen-infected site, HBP is released in the neutral granule or cytoplasm after being infected by bacteria, which aggravates the pneumonia patients' inflammatory reactions [31]. The 1,25-(OH)₂D₃ is an effective immunomodulator in the human body. An increase in its level will activate vitamin D₃ receptors to fight pathogens, while a decrease in its level indicates an increase of the pathogen content and the inflammatory reaction [32]. Therefore, the HBP levels decreased and the 1,25-(OH)₂D₃ levels increased in the combined group, which led to a decrease of the inflammatory factors in the children. Combined with the previous immune function results, the combined group eliminated a large number of pathogenic bacteria, the patients' immune systems recovered, and the inflammation was alleviated. The reduction of inflammation indicates that the treatment is safer, and a series of adverse reactions are also reduced, which is more conducive to

the recovery of children after the treatment. Therefore, the clinical indexes of the patients in the combined group recovered faster, and the total effective rates were higher after the treatment. However, we failed to investigate whether the parents were satisfied with the treatment, which is not conducive to our future improvement of the treatment methods. Therefore, in our future experiments, we need to investigate the post-treatment parent satisfaction, so as to further improve the treatment methods and promote the rehabilitation of children. We also need to study the immune molecular signaling pathway affected by multi-drug resistant bacteria

to discover the deeper molecular mechanism of the pneumonia caused by these bacteria.

To sum up, cefoperazone sulbactam sodium combined with meropenem has a better eradication effect on multidrug-resistant bacteria, and it can better improve the immune function of neonatal patients with pneumonia caused by multidrug-resistant bacteria.

Disclosure of conflict of interest

None.

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