Research Paper

Effect and Safety of Amoxicillin-Clavulanate Potassium and Ceftriaxone Combined with Pulmonary Physical Therapy on Neonatal Pneumonia

JING LI, DI ZHANG AND WENXIU YAO*

Department of Neonatology, The First Hospital of Qinhuangdao, Qinhuangdao, Hebei 066000, China

The main objective of this study was to determine the effect, safety and intestinal microecology of amoxicillin-clavulanate potassium, ceftriaxone combined with pulmonary physical therapy on neonatal pneumonia. A total of 180 neonatal pneumonia patients in our hospital were studied and divided into research group (n=90) and control group (n=90). The control group was treated with amoxicillin-clavulanate potassium and ceftriaxone and the study group was treated with pulmonary physiotherapy on the basis of control group. The treatment cycle was 7 d. The two groups were compared with total response rate, symptom resolution time, lung function index, inflammatory factor index, adverse reactions and the number of major probiotics in the intestine. The total effective rate of the research group was significantly higher than that of the control group, the symptom disappearance time of the research group was shorter than that of the control group and the lung function index was better than that of the control group. The inflammatory factor index, the incidence of adverse reactions was lower than that of the control group and the main probiotics in the intestinal tract of the research group was more than that of the control group ($p<0.05$). For neonatal pneumonia, on the basis of amoxicillin-clavulanate potassium and ceftriaxone, supplemented with pulmonary physical therapy, the effect is better, the safety is high and it can improve the lung function level of patients, reduce the level of inflammatory factors and balance the gut microbiome.

Key words: Amoxicillin-clavulanate potassium, ceftriaxone, pulmonary physiotherapy, neonatal pneumonia

Chronic Neonatal pneumonia refers to a lung infection that occurs within the first 28 d of life. The etiology may be related to bacteria, viruses, fungi or parasites. The common infectious bacteria are pneumococcus, *Staphylococcus aureus*, *Streptococcus* and *Escherichia coli*[1]. Based on the different causes, neonatal pneumonia is classified into two categories-Aspiration pneumonia and infectious pneumonia. The main routes of infection for aspiration pneumonia are amniotic fluid inhalation, breast milk inhalation and meconium inhalation. The clinical symptoms of neonatal pneumonia mainly include shortness of breath, cough, dyspnea and fever. Because neonates have weak immune function and poor resistance to germs, the disease develops rapidly and easily causes sepsis, meningitis, etc., which is one of the main causes of neonatal death[2]. Drugs for neonatal pneumonia mainly include antibiotics (such as penicillin's, cephalosporin's, aminoglycosides), antiviral drugs (such as acyclovir, oseltamivir), antifungal drugs (such as fluconazole, conazole) and supporting drugs (such as corticosteroids, analgesics), etc. In this study, amoxicillin-clavulanate potassium and ceftriaxone were selected as the drugs for neonatal pneumonia. Amoxicillin-clavulanate potassium is a combination drug and its main ingredients include amoxicillin and potassium clavulanate. Among them, amoxicillin is classified as a penicillin antibiotic, which has a strong broad-spectrum antibacterial effect and is generally used for a variety of bacterial infections. Potassium clavulanate is a beta (β)-lactamase inhibitor, which enhances the antibacterial effect by reducing the activity of β-lactamase. Ceftriaxone can kill a variety of bacteria, including pneumococcus, *Haemophilus influenzae*, *Streptococcus* and other common pneumonia pathogens. Studies have shown that pulmonary physical therapy has a better effect on neonatal pneumonia[3]. Based on this, we used

***Address for correspondence**
E-mail: lijingyoyo0730@126.com

amoxicillin-clavulanate potassium and ceftriaxone supplemented with pulmonary physical therapy to explore the curative effect and impact on children. The main purpose of this study is to determine the effect of single drug therapy and drug therapy combined with pulmonary physical therapy on newborns and to determine the difference between them.

MATERIALS AND METHODS

General information:

The 180 subjects involved in this study were all from neonatal pneumonia patients admitted to our hospital from January 2021 to December 2022. The group was divided into study group (n=90) and control group (n=90) by random grouping method. The research group included 48 males and 42 females, aged (4.62±1.87) d and gestational weeks are (39.45±1.21) w. The control group consisted of 46 males and 44 females, aged (4.61±1.88) d and gestational weeks are (39.42±1.2) w. There was no significant difference in the basic data between the two groups ($p>0.05$). The ethical committee of The First Hospital of Qinhuangdao approved this study with the ethical approval number of 20230018.

Inclusion criteria: All children met the clinical diagnostic criteria for neonatal pneumonia after being diagnosed by doctors in our hospital; the age was within 0-28 d; all the children were born at full term; the guardians knew the purpose of this study and signed the informed consent.

Exclusion criteria: Children with congenital heart disease; cerebral palsy, etc. and along with those children who are allergic to penicillin and cephalosporin are excluded from the study.

Research methods:

Control group: All patients were given basic treatment such as oxygen inhalation and nebulization. The control group received amoxicillin-clavulanate potassium and ceftriaxone on the basis of the basic treatment. The manufacturer of amoxicillin-clavulanate potassium used in this study is Zhuhai Federal Pharmaceutical Co., Ltd., whose approval number is H20092383. The 0.6 g of specification was used in this study, which includes 0.5 g amoxicillin and 0.1 g potassium clavulanate. Generally, the dose is adjusted according to the weight and condition of the child. The standard adopted in this study is 30 mg each time, intravenously injected 3 times a day, with an interval of 6-8 h between each time, continuously for 7 d. Ceftriaxone for injection is produced by Shenzhen China Resources Jiuxin Pharmaceutical Co., Ltd., with the approval number H20013198 and the specification is 0.5 g/bottle. The dose is also adjusted according to the weight and condition of the newborn. The standard adopted in this study is 80 mg/kg each time, intravenously injected once a day and the drug is used continuously for 7 d.

Research group: On the basis of the control group, pulmonary physiotherapy was supplemented. Pulmonary physiotherapy mainly includes turning over, percussion, suction nursing and so on. Turning over is mainly to formulate a scientific plan according to the amount of lung secretions in children. When there is a lot of a secretion in the lungs, one need to turn over for every 3 h. When the secretions are concentrated on the left side, one need to operate the right side lying position to expel the sputum and if the secretions are concentrated on the right side, the opposite method need to be done. Percussion is mainly through rhythmic tapping by nurses to help the sputum to fall off which was attached to the tube wall with the help of external force, so as to facilitate the newborn to discharge sputum. It should be noted that the palm is empty and the movement should be gentle. When the child exhales, use the strength of the wrist to tap the lungs. When tapping the front chest, you need to abduct the upper arm, while tapping the underarm, you need to raise the upper arm and when tapping between the shoulder blades, you need to retract the lower upper arm. Tapping on each part needs to be repeated 6-7 times, generally controlled within 10 min. During the whole process, the child's pulse, breathing, etc. need to be closely observed. Sputum suction nursing mainly involves inserting sputum suction device into the mouth and nasal cavity of the child respectively in a sterile environment to suck sputum and secretions. Suction pressure is generally controlled at 80 mmHg for 5 s. If the child develops cyanosis, the oxygen flow should be increased to 10 %-15 %.

Evaluation indicators and standards for research:

Evaluation of curative effect: After treatment, the curative effect of the two groups of patients was observed. Recovery category showed that cough, sputum, shortness of breath and other symptoms disappeared, lesions disappeared in the chest X-ray and there are no rales in the lungs. Improvement

category showed that cough, sputum, shortness of breath and other symptoms are improved, lesions in the chest X-ray are reduced and lung rales are relieved. In ineffective category, cough, sputum, shortness of breath and other symptoms are not improved or aggravated, the lesions in the chest X-ray do not change or expand and no change or increase in pulmonary rales.

Total effective rate=Recovery rate+Improvement rate

Evaluation of each index: Symptom disappearances time involves the disappearance time of cough, fever and pulmonary rales in children, the shorter the time, the better the therapeutic effect on children.

Pulmonary function indicators include Tidal Volume (V_T), Functional Residual Capacity (FRC) and peak volume ratio i.e., it is the ratio of Volume to Peak Expiratory Flow (VPEF) over total expiratory Volume (Ve) of the children were measured by tidal breathing method with the help of a pulmonary function tester. Each child was measured 5 times and recorded 20 tidal breaths and finally calculated the average value. After treatment, the higher the value of V_T, FRC and VPEF/Ve, the higher the pulmonary function level of newborns.

Inflammatory factors such as high sensitivity C-Reactive Protein (hs-CRP), Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) were mainly observed in peripheral venous blood of children. We collected the peripheral venous blood of the children and sent it to the clinical laboratory of our hospital to detect the indicators of inflammatory factors. After treatment, the smaller the values, the better the level of inflammation improved.

The main purpose of this study is to observe whether the children have adverse reactions such as vomiting, diarrhea, rash, leukopenia and eosinophilia during the medication process, the lower the number of adverse reactions, the higher the drug safety.

The number of main probiotics in the intestine includes *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Eubacterium* and *Enterobacter*. Observe the number of probiotics in the two groups of patients after treatment, the more the number, better the curative effect.

Statistical analysis:

In this study, data was processed by Statistical Package for the Social Sciences (SPSS) 22.0 software and t or χ^2 test was used and $p<0.05$ was considered statistically significant in the difference.

RESULTS AND DISCUSSION

Comparison of total response rate between the two groups was shown in Table 1. The total effective rate was 90 % in the research group which was higher than 77.78 % in the control group ($p<0.05$).

Comparison of symptom resolution time between the two groups was shown in Table 2. The time for symptom disappearance in the research group was shorter than that in the control group ($p<0.05$).

Comparison of lung function indexes between the two groups was shown in Table 3. The three lung function indexes in the research group were higher than those in the control group ($p<0.05$).

Comparison of inflammatory factors between the two groups was shown in Table 4. The three indexes of inflammatory factors in the research group were lower than those in the control group ($p<0.05$).

Comparison of Adverse Drug Reactions (ADRs) between the two groups was shown in Table 5. The incidence of ADRs in research group and control group were 3.33 % and 8.89 %, respectively ($p<0.05$).

Comparison of intestinal microecology was shown in Table 6. The number of main probiotics in the intestinal tract of the research group was higher than that of the control group ($p<0.05$).

TABLE 1: COMPARISON OF TOTAL EFFECTIVE RATE BETWEEN THE TWO GROUPS (n, $\bar{x}\pm s$)

Group	n	Markedly effective	Efficient	Invalid	Total effective rate
Research	90	42 (46.67 %)	39 (43.33 %)	9 (10 %)	90 %
Control	90	32 (35.56 %)	38 (42.22 %)	20 (22.22 %)	77.78 %
χ^2					6.126
p					<0.05

TABLE 2: COMPARISON OF SYMPTOM DISAPPEARANCE TIME BETWEEN THE TWO GROUPS (x̄±s)

Group	n	Cough disappearance time	Fever	Pulmonary rales disappearance time
Research	90	3.16±0.52	1.7±0.26	4.27±0.63
Control	90	4.82±0.56	2.79±0.35	6.16±0.74
t		3.524	5.526	4.782
p		<0.05	<0.05	<0.05

TABLE 3: COMPARISON OF PULMONARY FUNCTION INDEXES BETWEEN THE TWO GROUPS (x̄±s)

Group (n=90)	V_T (ml/kg)		FRC (ml/kg)		VPEF/Ve (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research	5.32±1.17	8.23±1.86	54.36±9.76	92.58±10.12	23.27±2.89	38.24±3.25
Control	5.32±1.18	6.94±1.56	54.41±9.78	78.38±9.56	23.31±2.91	31.92±3.18
t	0.213	4.448	0.235	4.128	0.228	4.338
p	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

TABLE 4: COMPARISON OF INFLAMMATORY FACTORS BETWEEN THE TWO GROUPS (x̄±s)

Group	n	hsCRP (mg/ml)		TNF-α (μg/ml)		IL-6 (pg/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research	90	28.27±2.92	7.42±1.85	2.98±0.63	0.61±0.07	18.27±1.82	8.34±1.17
Control	90	28.31±2.94	9.68±1.96	2.98±0.62	0.98±0.11	18.28±1.81	10.28±1.31
t		0.226	3.824	0.214	5.826	0.199	4.279
p		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

TABLE 5: COMPARISON OF ADRS BETWEEN THE TWO GROUPS (n, x̄±s)

Group	n	Vomit	Diarrhea	Rash	Leukopenia	Eosinophilia	Total incidence
Research	90	1	1	0	0	1	3.33 %
Control	90	2	2	1	1	2	8.89 %
χ^2							6.285
p							<0.05

TABLE 6: COMPARISON OF INTESTINAL MICROECOLOGY (CFU/g, x̄±s)

Group	*Lactobacillus*		*Bifidobacterium*		*Enterococcus*		*Eubacterium*		*Enterobacter*	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research	9.81±0.28	8.98±0.23	9.62±0.73	9.31±0.56	9.28±1.12	8.63±0.91	9.92±1.23	9.53±0.41	8.85±0.72	8.31±0.35
Control	9.82±0.28	8.24±0.22	9.63±0.72	8.79±0.48	9.27±1.13	8.21±0.86	9.92±1.22	9.18±0.38	8.86±0.73	8.12±0.33
t	0.235	1.79	0.232	1.69	0.282	1.56	0.263	1.43	0.268	1.24
p	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: CFU: Colony Forming Units

There are many pathogens in neonatal pneumonia, which mainly include bacteria, germs and fungi. The most common pathogens are bacteria, mainly includes *Streptococcus*, *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*. In addition to these bacteria, viruses and fungi are also the main causes of neonatal pneumonia. Common viruses include respiratory syncytial virus, adenovirus, etc., and the most common fungal infection is *Candida*. The current treatment for neonatal pneumonia is mainly based on antibiotics[4]. Studies have pointed out that amoxicillin-clavulanate potassium combined with ceftriaxone for neonatal pneumonia has good effect and high safety[5]. The reason for this conclusion is that bacteria can produce β-lactamase, but amoxicillin-clavulanate potassium can block the effect of β-lactamase, prevent the occurrence of resistance, which can cause the bacteria to become more sensitive to amoxicillin-clavulanate potassium and thus kill the pathogen quickly[6]. Although potassium clavulanate has no antibacterial function, its combination with amoxicillin can increase the antibacterial activity and improve the efficacy of the drug. Potassium clavulanate can prolong the half-life of amoxicillin and make the drug last longer in the human body[7]. Amoxicillin-clavulanate potassium can pass through human cell walls and cell membranes and enter the interior of bacterial cells to achieve the antibacterial effect. Amoxicillin-clavulanate potassium can treat various types of bacterial infections, including pneumococcus, *Haemophilus influenzae*, *Escherichia coli* and so on. Studies have shown that there is no interaction between amoxicillin-clavulanate potassium and most other drugs[8]. Therefore, in this study, ceftriaxone and amoxicillin-clavulanate potassium will not reduce the potency of the respective drugs. On the contrary, the synergistic mechanism improves the efficacy of the drug. Ceftriaxone is a third generation cephalosporin antibiotics that can be used for a variety of infections, but also for neonatal pneumonia. It kills bacteria by cutting off the pathway of cell wall synthesis. It can interact with target receptors or synthetase receptors of bacterial wall, thus cutting off the bacterial wall synthesis pathway, resulting in the collapse and death of bacterial wall. Moreover, ceftriaxone can inhibit the production of β-lactamase by bacteria and improve its antibacterial activity. Ceftriaxone has a certain anti-inflammatory effect, which can inhibit the occurrence of inflammation, thereby reducing the inflammatory response and tissue damage caused by pneumonia. At the same time, ceftriaxone can regulate the immune function of the body, improve the body's resistance and enhance the body's resistance to bacteria. Ceftriaxone can resist Gram-positive bacteria, Gram-negative bacteria and anaerobic bacteria, etc., and is widely used. Studies have found that ceftriaxone has a strong bactericidal effect on sensitive Gram-negative bacteria, a stable effect on lactamase and it has a low probability of drug resistance with very good therapeutic effect[9]. Some researchers pointed out that one of the ingredients in ceftriaxone is alkaline co-solvent sodium carbonate, which increases its hydrophilicity by increasing the dissociation level of acidic genes, so ceftriaxone is more effective than first-generation and second-generation cephalosporins. Ceftriaxone are more soluble and more likely to exert their drug effect after intravenous injection[10]. Sodium carbonate, as an alkaline substance, can neutralize the acidic part of ceftriaxone, making it more stable and soluble. At the same time, sodium carbonate can improve the water solubility of ceftriaxone, so it is easier for the human body to absorb the drug and rapidly exerts its function to achieve the required drug effect. Some researchers found that combining ceftriaxone with other conventional drugs in the treatment of neonatal pneumonia can improve its therapeutic effect[11].

Due to the narrow trachea of newborns, when inflammation occurs, it is easy to cause secretions that cannot be discharged causing respiratory obstruction in children. The core goal of pulmonary physical therapy is to remove secretions from the respiratory tract of children, reduce the retention of airway secretions and improve the level of lung ventilation. A controlled study showed that the heart rate, respiration and oxygen saturation of patients in the study group were better than those in the control group after using lung physical therapy[12]. May be, the reason was lung physical therapy can maintain a balance of oxygen partial pressure and water in the alveoli and play a role in the diffusion of lung tissue, thereby improving lung function.

In this study, the two groups used the same drugs and the study group was supplemented with pulmonary physical therapy, resulting in completely different results between the two groups. Our analysis was that the efficacy of the drugs was affected by the children's respiratory secretions or the secretions aggravate the levels of inflammatory factors and lung function indexes. Studies have also shown that the use of antibiotics in neonatal pneumonia may disrupt the balance of neonatal intestinal microecology and

cause neonatal infection or diarrhea[13]. From this perspective, the ADRs in this study may be related to the imbalance of intestinal microecology in children. Studies have confirmed that antibiotic treatment of neonatal pneumonia will have adverse effects on the intestinal flora and microecology of children[14]. Therefore, in the process of medication for neonatal pneumonia, we should also pay close attention to the intestinal microecology of children and we should choose different types of probiotics to adjust and balance the actual situation. In this study, patients in the study group had better intestinal microecology than those in the control group. The reason may be related to the improvement of respiratory tract function and lung function by pulmonary physical therapy, thus reducing the damage to intestinal tract caused by drugs. In spite of this, the overall level of intestinal microecology in the study group was not good and each index value was not ideal. Therefore, probiotics should be properly adjusted. The limitation of this study is that neonatal pneumonia was caused by several reasons. But in this study, neonatal pneumonia with different causes was not classified and the treatment methods were unified, which could not achieve symptomatic treatment. In this study, the cycle of different treatment methods for children is 7 d, which has certain limitations. Some children may be cured in 3 or 4 d, while others may need 10 s. This is related to the physical signs of different individuals, but it cannot say which treatment method is superior or inferior.

In this study, amoxicillin-clavulanate potassium and ceftriaxone combined with pulmonary physical therapy have a significant effect with high safety on newborns. However, it is ideal to adjust the intestinal microecological balance in children and probiotics can be considered for adjustment.

Conflict of interests:

The authors declared no conflict of interest.

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