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Clinical Therapeutic Effects of Amoxicillin/Clavulanate Potassium Administered by Different Methods on Recurrent Lower Respiratory Tract Infection in Children

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ABSTRACT

Objective: To evaluate the clinical therapeutic effects of amoxicillin/clavulanate potassium administered by different methods on recurrent lower respiratory tract infection in children.

Methods: A total of 110 children admitted to Department of Pediatrics, Suixi Hospital and diagnosed as recurrent lower respiratory tract infection from January 2017 to January 2019 were selected as the subjects. They were equally divided into control group and observation group using a random number table. Amoxicillin/clavulanate potassium was administered through routine intravenous infusion and sequential therapy for control group and observation group, respectively. The clinical efficacy, T-lymphocyte subsets, immunoglobulin (Ig) level and incidence rate of adverse reactions were compared between the two groups.

Results: The clinical overall response rate was higher in observation group than that in control group (94.54% *vs.* 78.18%) (χ^2=6.253, P=0.012). Cluster of differentiation 4 (CD4)$^+$/CD8$^+$, CD4$^+$ and CD3$^+$ were higher at the end of treatment than those before treatment in the two groups, but CD8$^+$ was lower than that before treatment. At the end of treatment, CD4$^+$/CD8$^+$, CD4$^+$ and CD3$^+$ increased in observation group compared with those in control group, while CD8$^+$ decreased compared with that in control group (P<0.05). Serum IgA, IgM and IgG were higher at the end of treatment than those before treatment in the two groups, but C-reactive protein (CRP) was lower than that before treatment (P<0.05). At the end of treatment, observation group had significantly raised serum IgA, IgM and IgG as well as significantly reduced CRP in comparison with those of control group (P<0.05). The incidence rate of adverse reactions was significantly lower in observation group than that in control group (7.27% *vs.* 27.27%) (χ^2=7.698, P=0.006).

Conclusion: Sequential therapy using amoxicillin/clavulanate potassium for recurrent lower respiratory tract infection in children can correct immune dysfunction and reduce adverse reactions with obvious efficacy and high safety.

KEYWORDS: amoxicillin; clavulanate potassium; sequential therapy; children; recurrent lower respiratory tract infection; clinical therapeutic effect; safety

INTRODUCTION

Recurrent lower respiratory tract infection is mainly seen in children aged 2-6 years old and is a common respiratory disease in the Pediatric Department, with a high incidence rate of about 20% [1]. It has complex pathogenesis, and its major cause is the reduced body immunity and resistance to pathogenic bacteria in children [2]. It was reported that the low immune function is closely associated with the recurrent lower respiratory tract infection in children [3]. The disease is mainly manifested as cough, nasal discharge, dyspnea,

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fever and other symptoms in clinical practice, which will cause a protracted course and recurrent attacks if not controlled and treated timely, thus seriously affecting the physical and mental health and the quality of life of children [4,5]. amoxicillin/clavulanate potassium is a kind of antibiotic that can effectively enhance the antibacterial activity of the body [6]. Sequential therapy is a treatment regimen in which intravenous administration is conducted at the beginning of the disease to repress the massive proliferation of bacteria in infected area, and then the administration route is changed after the disease has been improved. In this way, certain plasma concentration will be maintained continuously, realizing the purpose of sterilization *in vivo* [7]. At present, there are few studies on the treatment of recurrent lower respiratory tract infection in children using sequential therapy of amoxicillin/clavulanate potassium, and this protocol also lacks a theoretical basis in treating such disease. Therefore, this study aims to explore the efficacy and safety of sequential therapy of amoxicillin/clavulanate potassium in the treatment of recurrent lower respiratory tract infection in children.

MATERIALS AND METHODS

Subjects

A total of 110 children with recurrent lower respiratory tract infection admitted to Department of Pediatrics, Suixi Hospital from January 2017 to January 2019 were selected as the subjects. They were divided into control group and observation group using a random number table (n=55). In observation group, there were 30 males and 25 females aged 1-7 years old, with (4.05 ± 1.02) years old on average. Their course of disease was 1-14 months, with an average course of (7.23 ± 1.18) months. The annual onset frequency was 3-8 times, (4.84 ± 1.48) times on average. Moreover, there were 28 cases of bronchopneumonia and 27 cases of bronchitis. Control group had 28 males and 27 females aged 1-8 years old, with an average of (4.08 ± 1.05) years old. Their course of disease was 1-15 months, (7.35 ± 1.23) months on average. The annual onset frequency was 3-9 times, with an average of (4.92 ± 1.52) times. This group included 29 cases of bronchopneumonia and 26 cases of bronchitis. There was no significant difference in general data between the two groups (P>0.05).

Inclusion and exclusion criteria

Inclusion criteria: (1) Children who met the diagnostic criteria related to lower respiratory tract infection in the Diagnostic Criteria for Recurrent Respiratory Tract Infections in Children [8], (2) those who had clinical manifestations such as fever, cough, pulmonary rales and nasal discharge in different degrees, (3) those whose onset frequency of lower respiratory tract infection was more than twice each year, and (4) those who did not take antibacterial agents prior to the visit.

Exclusion criteria: (1) Children used immunodepressant at 30 days before admission, (2) those who were allergic to the drugs in this study, (3) those known to have bacteria resistant to amoxicillin/clavulanate potassium in the body, (4) those complicated with congenital pulmonary hypoplasia, congenital bronchial disease, infectious shock, septicemia or immunodeficiency disease, or (5) those complicated with cardiac, hepatic or renal insufficiency.

Treatment methods

After admission, all the children received relevant examinations and basic symptomatic treatments, including maintaining electrolyte balance, relieving cough and reducing sputum, and bringing down a fever. In control group, amoxicillin/clavulanate potassium injection (North China Pharmaceutical Company Ltd., NMPN: H20054213) was routinely infused intravenously for 7-10 consecutive days (100 mg/kg for twice each day) until all the clinical symptoms disappeared. In observation group, sequential therapy of amoxicillin/clavulanate potassium was used. Specifically, amoxicillin/clavulanate potassium injection was infused intravenously for 3 consecutive days (100 mg/kg, twice each day) at the beginning of the onset. After the disease condition of the children was stable, the regimen was changed to oral administration of amoxicillin/clavulanate potassium granules (Jiangsu Simcere Pharmaceutical Co., Ltd., NMPN: H10950244) 15 mg/kg·d at 2 equal doses) for 5 consecutive days.

Observation indices

Clinical efficacy: Treatment effects in the two groups were evaluated in accordance with the response evaluation criteria stipulated in the *Guidance for Clinical Trials of Anti-bacterial Drugs* [9] at 10 d after treatment. Ineffective: the clinical symptoms and signs were not improved or were aggravated after over 3 days of drugs administration, and the examination result was abnormal. Markedly effective: the clinical symptoms and signs were obviously improved, and the examination result was normal. Cured: all the clinical symptoms and signs disappeared

completely, with normal examination result. Overall response rate = (cured cases + effective cases)/total cases × 100%.

Measurement of immune indices: Fasting peripheral venous blood of the upper limb was drawn from children in the two groups before treatment and at the end of treatment (10 d after treatment), and a flow cytometer was used to detect T-lymphocyte subsets [cluster of differentiation 3 $(CD3)^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$). Part of venous blood was centrifuged at 3000 r/min for 15 min to get the supernatant, and then immunity transmission turbidity [10] was used to determine C-reactive protein (CRP), immunoglobulin A (IgA), IgM and IgG levels.

Adverse reactions: Adverse reactions occurred after treatment in the two groups, including diarrhea, asthma, nausea and vomiting and phlebitis, were recorded.

Statistical analysis

SPSS 21.0 software package was employed for statistical analysis. Quantitative data were expressed as mean ± standard deviation ($\bar{x}$ ± s), and *t*-test was used for independent samples. Numerical data were expressed as case (n) or percentage (%) and examined by χ^2 test. P<0.05 suggested that the difference was statistically significant.

RESULTS

Clinical therapeutic effects

The clinical overall response rate of children was 94.54% in observation group, which was higher than that in control group (78.18%). The difference was statistically significant (P<0.05) (Table 1).

Table 1. **Clinical therapeutic effects [n (%)]**

Group	Cured	Markedly effective	Ineffective	Overall response rate
Observation (n=55)	30 (54.54)	22 (40.00)	3 (4.08)	52 (94.54)
Control (n=55)	23 (41.82)	20 (36.36)	12 (25.00)	43 (78.18)
χ^2				6.253
P				0.012

T-lymphocyte subsets

No significant differences were found in $CD4^+/CD8^+$, $CD8^+$, $CD4^+$ and $CD3^+$ between the two groups of children before treatment (P>0.05). $CD4^+/CD8^+$, $CD4^+$ and $CD3^+$ were higher at the end of treatment than those before treatment in the two groups of children, while $CD8^+$ was lower compared with that before treatment. Moreover, at the end of treatment, $CD4^+/CD8^+$, $CD4^+$ and $CD3^+$ significantly increased, but $CD8^+$ significantly decreased in observation group in contrast with those in control group (P<0.05) (Table 2).

Table 2. **T-lymphocyte subsets ($\bar{x}$ ±s)**

Group	$CD4^+/CD8^+$		$CD4^+$ (%)		$CD8^+$ (%)		$CD3^+$ (%)	
	Before treatment	At the end of treatment	Before treatment	At the end of treatment	Before treatment	At the end of treatment	Before treatment	At the end of treatment
Observation (n=55)	1.15±0.32	1.88±0.52[a]	29.28±4.05	47.35±5.56[a]	28.89±3.46	21.63±2.34[a]	58.10±4.85	73.65±6.54[a]
Control (n=55)	1.10±0.30	1.49±0.46[a]	28.98±3.98	40.73±5.48[a]	28.65±3.38	24.35±2.67[a]	57.85±4.78	65.47±6.23[a]
t	0.845	4.166	0.392	6.290	0.368	5.682	0.272	6.716
p	0.399	<0.001	0.696	<0.001	0.713	<0.001	0.756	<0.001

[a]P<0.05 *vs.* before treatment within the same group.

Serum Ig levels

There were no statistically significant differences in serum IgA, IgM, IgG and CRP between the two groups before treatment (P>0.05). Serum IgA, IgM, IgG increased, while CRP decreased at the end of treatment compared with those before treatment in the two groups (P<0.05). At the end of treatment, the observation group had higher serum IgA, IgM, IgG and CRP but significantly lower CRP than control group (P<0.05) (Table 3).

Adverse reactions

The incidence rate of adverse reactions of children was higher in control group than that in observation group (27.27% *vs.* 7.27%) (χ^2=7.698, P=0.006) (Table 4).

Table 3. Serum Ig levels ($\bar{x}$ ± s, g/L)

Group	IgA		IgM		IgG		CRP	
	Before treatment	At the end of treatment	Before treatment	At the end of treatment	Before treatment	At the end of treatment	Before treatment	At the end of treatment
Observation (n=55)	0.48±0.16	1.46±0.32[a]	0.93±0.35	1.80±0.58[a]	7.54±3.27	13.48±2.95[a]	14.83±5.62	9.25±2.63[a]
Control (n=55)	0.45±0.14	1.03±0.28[a]	0.90±0.32	1.36±0.47[a]	7.50±3.25	11.35±2.87[a]	14.67±5.53	10.48±2.72[a]
t	1.046	7.499	0.469	4.371	0.064	3.838	0.151	2.411
p	0.298	<0.001	0.640	<0.001	0.949	<0.001	0.881	0.018

[a]P<0.05 *vs.* before treatment within the same group.

Table 4. **Adverse reactions [n (%)]**

Group	Phlebitis	Diarrhea	Nausea and vomiting	Asthma	Incidence rate of adverse reactions
Observation (n=55)	0 (0.00)	1 (1.82)	3 (5.45)	0 (0.00)	4 (7.27)
Control (n=55)	5 (9.09)	3 (5.45)	5 (9.09)	2 (3.64)	15 (27.27)
χ^2					7.698
P					0.006

DISCUSSION

Recurrent lower respiratory tract infection in children is a common bacterial infectious disease clinically. Among the complicated and diversified reasons, the main one is that the attack of external pathogenic bacteria cannot be resisted completely due to the reduction of body immunity in children [11]. The recurrent feature of this disease has brought pain to children, and the failure of timely treatment will worsen the condition of the disease, cause such symptoms as dyspnea, cyanosis and asthmatic suffocating, and even induce respiratory failure, threatening the life safety of children. amoxicillin/clavulanate potassium, a commonly used semi-synthetic penicillin antibiotic in clinical practice, consists of amoxicillin and clavulanate potassium and has an extremely strong bactericidal power [12]. Clinical research has confirmed that amoxicillin/clavulanate potassium has a strong bactericidal effect on bacterial strains in the lower respiratory tract [13]. In the past, the routine intravenous infusion of amoxicillin/clavulanate potassium was utilized for the treatment of recurrent lower respiratory tract infection in children, which resulted in a long hospital stay, high expenses, poor treatment efficacy and many adverse reactions. With the development of the medical technologies in recent years, sequential therapy of amoxicillin/clavulanate potassium has been applied in clinical practice extensively. Some domestic scholars have found that the therapy has an obvious effect on respiratory tract infections [14,15]. Therefore, the effective treatment method is very important for children diagnosed with such diseases. In this study, sequential therapy of amoxicillin/clavulanate potassium was conducted to observe its clinical efficacy and safety in treatment of recurrent lower respiratory tract infection in children.

This study showed that the clinical overall response rate in observation group was 94.54%, significantly higher than that in control group (78.18%), suggesting that sequential therapy of amoxicillin/clavulanate potassium has a notable curative effect on recurrent lower respiratory tract infection in children, and can improve the overall response rate of the treatment. The study of Qi [16] revealed that sequential therapy of amoxicillin/clavulanate potassium produced a remarkable effect on bronchopneumonia, proving that amoxicillin/clavulanate potassium has high-efficient antibacterial activity. The intravenous infusion of amoxicillin/clavulanate potassium in the initial stage of infection can effectively control the bacterial reproduction in the respiratory tract, but it will intimidate most children, and the fear to injection will cause poor compliance of children, thus affecting the treatment effect. However, after the disease condition is stabilized and improved, the regimen can be changed to oral administration of amoxicillin/clavulanate potassium, which can not only enhance the compliance of children with treatment but also maintain a certain plasma concentration, thereby realizing sterilization in the body and further improving the clinical efficacy. The causes of recurrent lower respiratory tract infection in children are complicated, of which the abnormal immune function of children is associated with the immature immune system. When IgA and IgG levels are low, the physiological immune function of

children will be in a low state and vulnerable to attacks of viral and bacterial infections, thus leading to respiratory tract infections [17,18]. Cellular and humoral immunities in children with recurrent respiratory tract infection are weaker than those in normal children. It was revealed in this study that at the end of treatment, peripheral blood T-lymphocyte subsets and serum IgA, IgM, IgG and CRP were higher in observation group than those in control group (P<0.05), suggesting that sequential therapy of amoxicillin/clavulanate potassium may obviously enhance the immunocompetence of children with recurrent lower respiratory tract infection. The above results indicate that sequential therapy of amoxicillin/clavulanate potassium may stimulate the specific and non-specific immunities in children to regulate the quantity of T-lymphocyte subsets, effectively reduce IgA, IgM and CRP levels and promote secretion of IgG at the same time, thus improving lymphocyte proliferation and Ig levels, and finally enhancing the body immunity of children. Relevant references reported that sequential therapy of amoxicillin/clavulanate potassium has an obviously promoting effect on children with a low immunity, and it can be extensively used for acute attacks of respiratory tract infection in children and chronic bronchitis in the elderly, whose treatment efficacy is consistent with that in this study [19]. In addition, it was found that the incidence rate of adverse reactions in observation group was 7.27%, obviously lower than that in control group (27.27%), suggesting that sequential therapy of amoxicillin/clavulanate potassium can effectively inhibit nausea and vomiting, diarrhea, asthma and other adverse reactions, make the best use of the drug effect, reduce infections and reach the best treatment efficacy. Moreover, no phlebitis case occurred in observation group, but there were 5 cases of phlebitis in control group, indicating that long-time intravenous infusion increases the risk of phlebitis, further demonstrating that sequential therapy of amoxicillin/clavulanate potassium is safe and effective, and alleviates the pain caused by persistent intravenous infusion. The results of this study better manifested the advantages of sequential therapy of amoxicillin/clavulanate potassium, as follows [20]: (1) The therapy can reduce the pain brought by long-term venipuncture and the occurrence of adverse reactions, and improve the compliance of children with treatment, thus enhancing the treatment efficacy. (2) It enables the children to be discharged from hospital as early as possible, then reducing the incidence rate of nosocomial infection. (3) It can save the hospitalization costs and medical expenses, thus reducing the economic burden of children's family.

In conclusion, sequential therapy using amoxicillin/clavulanate potassium for recurrent lower respiratory tract infection in children has evident efficacy and high safety. Besides, it can correct the immune dysfunction of children and reduce adverse reactions.

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