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Original Article

Cefathiamidine combined with azithromycin in the treatment of lower respiratory tract infection in children

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Abstract: Objective: The purpose of this study was to investigate the clinical effect of cefathiamidine combined with azithromycin (AZM) in the treatment of lower respiratory tract infection (LRTI) in children. Methods: A total of 100 children with LRTI who were admitted to our hospital were selected and divided into the control group (CG, n=49) and the observation group (OG, n=51) according to different therapeutic schedules. Thereinto, the CG was treated with cefathiamidine and the OG was treated with cefathiamidine combined with AZM. The two groups were compared in total effectiveness, time of disappearance of signs (cough, respite, pulmonary rales and recovery to normal temperature), hospital stay, incidence of adverse reactions after medication and treatment cost. Results: The total effectiveness was 71.42% in the CG, which was much lower than 92.15% in the OG, showing a statistically significant difference (X^2=5.617, P < 0.05). The indicators of cough, respite, pulmonary rales and recovery to normal temperature, in the OG, were much better than those of the CG after treatment (P < 0.05). After treatment, the incidences of gastrointestinal reaction and rash were respectively 5.88% and 3.92% in the OG, much lower than 10.20% and 8.16% in the CG, showing a statistically significant difference (P < 0.05). The negative conversion rate of Gram bacteria was 90.19% in the OG and 81.63% in the CG after treatment (X^2=4.535, P < 0.05). Conclusion: The clinical effect of cefathiamidine combined with AZM was much better than that of the single medication in the treatment of children with LRTI. Besides, cefathiamidine combined with AZM had higher bacterial eradication rate and lower incidence of adverse reactions in the treatment of children with LRTI, which is worthy of clinical promotion and application.

Keywords: Cefathiamidine, azithromycin, lower respiratory tract infection in children

Introduction

Lower respiratory tract infection (LRTI) in children is very common in clinical pediatrics and is usually treated with antibiotics. However, due to the misuse of antibiotics, its clinical application has been more strictly managed and controlled [1]. According to the World Health Organization, LRTI in children is the leading cause of death in children under five years of age [2]. Generally, fungal pathogens include Gram-negative bacteria, *Klebsiella pneumoniae* (KNP), *Escherichia coli* (*E.coli*) and *Haemophilus influenzae* (HiB), *etc*. [3], which are the pathogenic bacteria in 15%-40% of pneumonia and capillary bronchitis. There are some other common bacteria, such as influenza virus, parainfluenza virus, human metapneumovirus and adenovirus, *etc*. Some children are infected by multiple viruses.

At present, there are more than 1,200 viral-pathogens [4]. More and more pathogenic viruses can be detected with the continuous improvement of detection technology. Different kinds of viruses have different genetic material, mainly including DNA virus, RNA virus and protein virus [5]. Cefathiamidine is a β-lactam antibiotic mainly used for the treatment of bronchitis, pneumonia and a variety of bacterial diseases. It has been widely applied in clinical treatment for its advantages of dealing with a wide antibacterial spectrum, strong antibacterial action, small side effects and high blood concentration, *etc*. [6] Azithromycin (AZM) is a macrolide antibiotic, with a high bactericidal

activity against Gram bacteria, Gram-negative bacteria and *Staphylococcus aureus*, *etc.* [7]. As a patented product with independent intellectual property rights in China, cefathiamidine has a high bactericidal activity to staphylococcus and enterococcus. Studies have found that cefathiamidine has a strong bacteriostatic effect on most Gram-positive cocci, and the mechanism of action is that it acts on the cell wall of the bacterial septum and affects the synthesis of the cell wall of the sensitive bacteria, thus destroying the synthesis of the bacterial mucin, blocking the cross connection of mucopeptide and blocking the formation pathway of the complete cell wall, thus achieving a good antibacterial effect [8]. Some data show that cefathiamidine and AZM respectively, achieved significant effect in the treatment of LRTI in children [9]. The purpose of this study was to investigate the clinical effect of cefathiamidine combined with AZM in the treatment of LRTI in children.

Materials and methods

Clinical data

A total of 100 children with LRTI admitted to our hospital from November 2018 to October 2019 were selected for retrospective analysis and divided into the control group (CG, n=49, treated with cefathiamidine) and the observation group (OG, n=51, treated with cefathiamidine combined with AZM) according to different therapeutic schedules. Inclusion criteria: The patients who were definitely diagnosed with LRTI [10] through bacteriological examination; those without complications; and those who cooperated with treatment and were successfully discharged after treatment were included. Exclusion criteria: This study excluded patients with respiratory failure or heart failure; those allergic to drugs used in this study; and those with severe liver and kidney dysfunction. This study has been approved by the Ethics Committee of Fuyang District Hospital of Traditional Chinese Medicine of Hangzhou, and all family members and patients were informed and signed an informed consent.

Methods

Examination methods: The specimens of all patients were collected on the day of admission or in the next morning after admission. These specimens were put in sterile test tubes containing normal saline and stored in the freezer at -80°C. Experimental materials and reagents: DNA/RNA nucleic acid extraction kit, RT-PCR kit, multiple PCR reagent for respiratory virus, multiple PCR reagent for fungal pneumonia, DEPC treated water, agarose and TBE buffer, *etc*.

Key instruments: (1) Disposable tips (with filter element); (2) PCR tubes; (3) CORNING centrifuge tubes (15 ml, MEXICO); (4) centrifuge tubes (1.5 ml, 2.0 ml); (5) Sartorius electronic scale; (6) BIO-RAD electrophoresis apparatus; (7) ice machine (Cainelius); (8) Millipore hyperpure water system; (9) water bath; (10) microwave oven; (11) ultra cold storage freezer (Haier); (12) vortex mixer; (13) high-pressure steam sterilization bath; (14) EP tube, head and pipette; (15) horizontal electrophoresis apparatus; (16) Bechman high-speed refrigerated centrifuge; (17) Eppendorf centrifuge; (18) biosafety cabinet; (19) GelpocXR motored molecular imaging system (BIO-RAD, America); (20) OIAxcel automated DNA/RNA analysis system (QIAGEN, Germany); (21) PCR (Applied Biosystems, America); (22) 516 superfine flocking nasopharyngeal swab for children.

Experimental methods: The specimens were taken out for automatic melting. After complete vibration, 200 μl of specimens were put into the centrifuge tube (1.5 ml) and centrifuged. Eight μl of nucleic acids were put into PCR tubes. Then, 3 μl of FEPC-treated water and 1 μl of random hexamers were added. After centrifugation and mixing, the tube was placed at 80°C for 3 min, and then cooled for 2 min before centrifugation. Four μl of 5XRTbuffer, 2 μl of 10mMdNTP, 1 μl of Rname inhibitor and 1 μl of Reverse Transcriptase were added. After centrifugation and mixing, the tube was successively placed at 37°C and 94°C and on the ice for 90 min, 2 min and 2 min respectively. cDNAwasobtainedthroughcentrifugationandstored in the refrigerator of 4°C. PCR negative control group: sterile deionized water; PCR positive control group: mixture of 15 pathogenic bacteria through quality control and clone. Autoanalyzer was used to analyze above PCR amplification products and Alignment Marker. Q1 Axcel BioCaculator was used to analyze the results.

Treatment methods: A total of 0.2 g cefathiamidine was added into 100 ml of sodium chloride and intravenously dripped into the CG twice a

Table 1. Comparison of clinical data between the two groups ($\bar{x} \pm s$)/[n]

Clinical data		Observation group (n=51)	Control group (n=49)	t/X^2	*P*
Gender	Male	23	25	0.351	0.553
	Female	28	24		
Average age (years)		3.31 ± 1.19	3.42 ± 1.21	0.458	0.648
Admission conditions (%)	Mild	45.90	48.97	0.753	0.568
	Moderate	25.49	26.53		
	Severe	29.41	24.48		

day. On the basis of the treatment in the CG, 0.5 g AZM was added into sodium chloride and intravenously dripped into the OG. The dripping speed was 45 min^{-1}. The treatment lasted for 7 d.

Therapeutic evaluation

According to the *Guiding Principles of Clinical Use of Antibiotics* issued by the Ministry of Health [11], the therapeutic effect was divided into cure, marked effectiveness, effectiveness and ineffectiveness. Cure refers to the disappearance of clinical symptoms and adverse reactions. Marked effectiveness refers to obvious improvement of clinical symptoms and adverse reactions. Effectiveness refers to the improvement of adverse reactions and clinical symptoms. Ineffectiveness means that the disease worsened after treatment or there is no significant difference before and after treatment. Markedly effective rate = (cure + marked effectiveness)/total number of cases × 100%. The therapeutic effect of microbes was effective if Gram bacteria were eliminated after treatment; and ineffective if Gram bacteria failed to be alleviated after treatment. The following indicators of the two groups were recorded: time of disappearance of cough, respite and pulmonary rales, body temperature, hospital stay and incidence of adverse reactions.

Statistical analysis

SPSS 13.0 statistical software was used for data analysis. The enumeration data were compared between groups through χ^2 test. The measurement data were expressed as mean ± standard deviation (mean ± SD) and compared between groups through t test. ($P < 0.05$) indicated that the difference was statistically significant [12].

Results

Comparison of clinical data between the two groups

The OG had 51 patients, including 23 males and 28 females, aged 4.9 months to 7 years, with an average age of (3.31 ± 1.19) years and the course of disease of 1-6 d. The CG had 49 patients, including 25 males and 24 females, aged 4.8 months to 8 years, with an average age of (3.42 ± 1.21) years and the course of disease of 2-7 d. The clinical data of the two groups showed no statistical differences, indicating the groups are comparable ($P > 0.05$), as shown in **Table 1**.

Total clinical effectiveness of the two groups

The ineffective rate of the two groups was 0.00% after treatment ($P > 0.05$). After treatment, the cure rate, markedly effective rate and effective rate were respectively 51.02%, 20.40% and 28.57% in the CG; which was much lower than 68.68%, 23.52% and 7.84% in the OG ($P < 0.05$), as shown in **Table 2**.

Changes in signs of the two groups after treatment

There was a statistical difference in cough, respite, pulmonary rales, time of recovery to normal temperature and hospital stay between the two groups after treatment ($P < 0.05$). This verified that combined treatment used in the OG could effectively shorten the hospital stay and the time of recovery of signs, as shown in **Figure 1**.

Incidence of adverse reactions

After treatment, Gram-positive cocci became negative in the two groups. The bacterial eradi-

Table 2. Comparison of total clinical effectiveness between the two groups after treatment [n (%)]

Group	n	Cure	Marked effectiveness	Effectiveness	Ineffectiveness	Total effectiveness
CG	49	25 (51.02)	10 (20.40)	14 (28.57)	0 (0.00)	71.42
OG	51	35 (68.62)	12 (23.52)	4 (7.84)	0 (0.00)	92.15
X^2						5.617
P						< 0.05

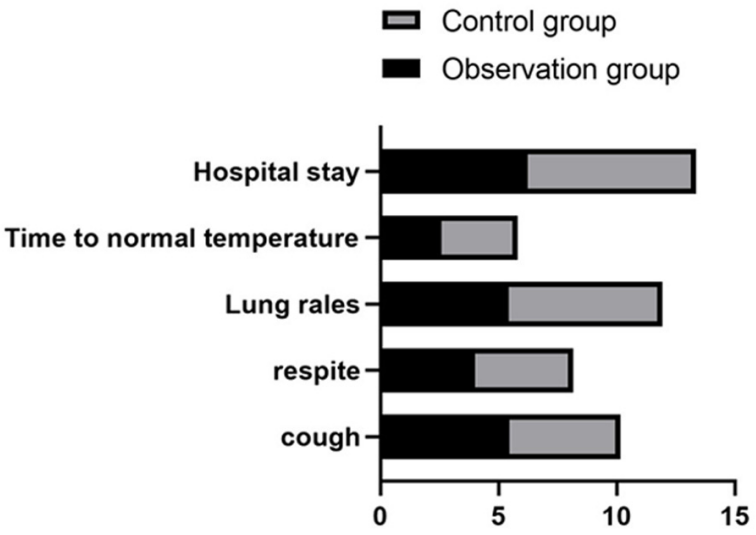

Figure 1. Comparison of changes in clinical signs between the two groups. The time of disappearance of cough, respite and pulmonary rales, the time of recovery to normal temperature and hospital stay in the OG were much shorter than those in the CG, showing statistical difference ($P < 0.05$). This verified that cefathiamidine combined with AZM could effectively shorten the time of recovery of signs.

Table 3. Comparison of incidence of adverse reactions after treatment in both groups [n (%)]

Item	OG (n=51)	CG (n=49)	X^2	*P*
Gram bacteria (becoming negative)	46 (90.19)	40 (81.63)	4.535	0.05
Gastrointestinal reaction	3 (5.88)	5 (10.20)	4.318	0.05
Rash	2 (3.92)	4 (8.16)	3.206	0.05

cation rate was 56.86% in the OG, much higher than 53.06% in the CG, showing statistically significant difference ($P < 0.05$). There was a statistical difference in incidences of gastrointestinal reaction and rash between the OG and CG ($P < 0.05$), as shown in **Table 3**.

Discussion

With the continuous development of medical technology, the detection technique for all pathogens has been constantly improved and supplemented. Currently, most pathogens can be detected through the existing technology, but the pathogens are still unclear for 30% of patients with respiratory tract infection (RTI) [13]. Common pathogens and fungi generally include *Enterobacter cloacae*, *Pseudomonas aeruginosa*, KNP, *E.coli*, *Enterobacter aerogenes*, *Proteus-bacillus vulgaris* and *Pseudomonas fluorescens*, *etc*. [14]. Respiratory issuesmay be induced by mycoplasma pneumoniae infection. However, there is no agreement on these reports due to the difference in seasonal conditions, experimental conditions and research methods, *etc*. Studies have shown that patients of all ages may suffer from mycoplasma pneumoniae infection [15], but clinically, the detection of mycoplasma pneumoniae infection is limited. Serological examination is usually performed, but there may be a false negative error. In addition, the high antibody titer may last for a long time after mycoplasma pneumoniae infection. Even if this infection is not caused by mycoplasma pneumoniae, the mycoplasma pneumoniae infection may show positive in this examination if the children were infected with mycoplasma pneumoniae before this time. This may be one of the main reasons for higher false positive rates of mycoplasma pneumoniae infection in clinical practice and also one of the causes for higher incidence of mycoplasma pneumoniae infection in literature [16]. Cefathiamidine is a new derivative of semisynthetic cephalosporins, with less adverse reactions and stronger bactericidal effect [17]. It mainly

acts on the septal cell walls of bacteria and it has good bactericidal activity to Gram-positive cocci and some Gram-negative bacilli. Cefathiamidine especially has a strong bactericidal effect on *Staphylococcus aureus* and *Enterococcus*. AZM is a common drug used for the clinical treatment of RTI. It can combine with other drugs to achieve a more significant effect. Due to the high drug resistance rate of *Streptococcus pneumoniae* to AZM, cephalosporin antibiotics are often combined. Previous studies have mostly used cefthiamidine or AZM alone, or azithromycin combined with other drugs in the cephalosporin family, such as ceftriaxone, cefuroxime sodium, *etc*., but there are few reports on AZM combined with cefthiamidine. This study compared the efficacy and safety of cefthiamidine and AZM either alone or in combination, so as to provide evidence for clinical rational drug use [18].

This study showed that the total effectiveness was 92.15% in the OG, which is much higher than 71.42% in the CG in LRTI patients. The difference showed statistical significance ($P < 0.05$) indicating combined treatment is superior in its efficacy. Some studies indicated that acute lower respiratory tract infection (ALRTI) in children mainly occurs in lower respiratory tract, trachea, bronchus and lung tissues. The main causes were inflammation and infection. This disease was acute and the course was short. Antibiotics were usually used for this disease in clinical practice [19, 20]. At present, the misuse of antibiotics is widespread, which leads to the drug resistance of bacteria to antibiotics. According to this study, ALRTI in children was mainly caused by Gram-negative bacteria and KNP was the main pathogen causing ALRTI in children. In Gram-positive bacteria, *Streptococcus pneumoniae* is still a major cause for ALRTI in children. Ampicillin and cefradine cannot effectively control these pathogens any more. KNP, *E.coli* and HiB are resistant to these two drugs [19, 21-24]. In this paper, the time of disappearance of cough, respite and pulmonary rales in the OG treated with AZM combined with cefathiamidine was much shorter than that in the CG ($P < 0.05$) and the time of recovery to normal temperature and hospital stay in the OG were shorter than those in the CG ($P < 0.05$). After treatment, the negative conversion rate of Gram bacteria was 90.19% in the OG, much better than 81.63% in the CG ($P < 0.05$). The incidences of rash, gastrointestinal reaction and other adverse reactions in the OG were much lower than those in the CG, showing statistical difference ($P < 0.05$). Both the OG and CG had good cure rates after corresponding treatment of adverse reactions. This study is a retrospective non-randomized controlled study with inherent biases, including a short median follow-up time, a small sample size, and the samples are from a single center, making the conclusions of the study of limited value; indicating a need to be confirmed by a larger sample prospective randomized controlled trial.

In conclusion, cefathiamidine combined with AZM can effectively eradicate the bacteria and enhance the cure rate in treatment of LRTI caused by Gram-positive cocci. Besides, the combination of these two drugs also reduces the incidence of adverse reactions. Therefore, this drug combination is worthy of clinical promotion and application.

Disclosure of conflict of interest

None.

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