Therapeutic Effect of Ambroxol Hydrochloride in Conjunction with Azithromycin in Treating *Mycoplasma pneumoniae* Pneumonia in Children

P. LI, W. LI, P. AO, GUANWEI DONG, S. LUO, YI LUO, Z. XIU, DANYU YAN[1], HONG QAIO[1] AND DEMAO MAO*

Department of Radiology, [1]Department of Paediatric, First People's Hospital of Longquanyi District, Chengdu, Sichuan Province 610100, China

To observe the therapeutic effect and changes in chest computed tomography signs in treating *Mycoplasma pneumoniae* pneumonia in children with ambroxol hydrochloride in conjunction with azithromycin. From November 2021 to November 2023, a total of 70 children diagnosed with *Mycoplasma pneumoniae* pneumonia were admitted to our hospital. These children were randomly assigned to either the control group or the observation group, with equal distribution of 35 cases in each group. Oral azithromycin was administered to the control group for 5 consecutive days, while the observation group received a combined treatment of azithromycin for 5 consecutive days and ambroxol hydrochloride for 7 consecutive days. A comparison was made between the two groups in terms of the time needed for temperature recovery, cough resolution, and disappearance of lung rales. Additionally, the comparison of various chest computed tomography signs before and after 7 d of treatment was conducted between the two groups. The incidence of adverse reactions during the treatment period was also recorded and compared. The observation group showed a remarkably shorter duration for temperature recovery, cough resolution, and disappearance of lung rales compared to the control group ($p<0.05$). Additionally, the overall treatment efficacy rate was notably higher in the observation group, reaching 94.29 %, and significantly surpassed the control group's rate of 77.14 % ($p<0.05$). During the treatment period, both groups of patients experienced adverse reactions such as rash, nausea/vomiting, and abdominal pain, with no remarkable disparity in the incidence of adverse reactions between the control group (17.14 %) and the observation group (20.00 %) ($p>0.05$). The combination therapy of ambroxol hydrochloride and azithromycin offers substantial therapeutic benefits for treating *Mycoplasma pneumoniae* pneumonia in children. It effectively reduces the duration of symptoms and signs, facilitates the recovery of lung lesions, and poses no notable risk of adverse reactions.

Key words: Ambroxol hydrochloride, azithromycin, *Mycoplasma pneumoniae* pneumonia, antibiotics

In children, *Mycoplasma pneumoniae* (*M. pneumoniae*) Pneumonia (MPP) is a frequently encountered infectious disease caused by *M. pneumoniae*. This bacterium can lead to infections in both the upper and lower respiratory tracts, presenting symptoms such as cough, wheezing, and difficulty breathing[1,2]. In infants and preschool children, MPP exhibits a high incidence rate, susceptibility, and contagiousness[3,4]. Despite its tendency to resolve naturally, the significance of treatment for MPP persists in clinical practice. Widely recognized as a macrolide antibiotic, azithromycin is extensively utilized for the management of respiratory tract infections and bacterial infections affecting the skin and soft tissues. It is regarded as the preferred initial treatment for MPP. Binding to the 50S ribosomal subunit, azithromycin hinders the crucial process of transpeptidation and Ribonucleic Acid (RNA)-dependent protein synthesis, effectively achieving the purpose of anti-mycoplasma. Nonetheless, there are situations where the utilization of azithromycin alone may not yield notable improvement in symptoms and signs, potentially causing enduring symptoms like a persistent cough and unresolved wheezing. The long-term administration of

***Address for correspondence**
E-mail: mao15008455148@163.com

azithromycin raises the risk of drug resistance development[5,6]. As a result, it becomes essential to explore the combined application of different medications to optimize treatment effectiveness. In its capacity as an expectorant, ambroxol hydrochloride swiftly acts on specific locations within the human body. It effectively reduces mucus viscosity, enhances the function of bronchial cilia, and facilitates the smooth discharge of mucus, simultaneously exerting an anti-inflammatory effect[7,8]. The effectiveness of ambroxol hydrochloride in treating respiratory diseases like childhood bronchial asthma and bronchitis has been supported by various studies[9,10]. In light of this, our hypothesis proposes that the combined use of ambroxol hydrochloride and azithromycin can heighten the inhibitory effects on *M. pneumoniae*, resulting in symptom improvement and accelerated recovery. Furthermore, chest Computed Tomography (CT), a valuable imaging tool, enables the visualization of the localized distribution, range, and extent of lung lesions. By investigating the effect of combination therapy on chest CT signs in children with MPP, it becomes possible to conduct a thorough and unbiased evaluation of treatment effectiveness, offering valuable insights for guiding clinical practice. From November 2021 to November 2023, a total of 70 children with a confirmed diagnosis of MPP were selected as the subjects for this study. The control group, consisting of 19 males and 16 females, had an average age of (5.12±1.60) y, within an age range of 3 y-11 y. Similarly, the observation group included 18 males and 17 females, between the ages of 3 y to 12 y, with an average age of (5.31±1.66) y. Crucially, there were no statistically significant variations in age and gender between the two groups ($p>0.05$), confirming their comparability. Clinically diagnosed with MPP[11]; no prior treatment with any medications before diagnosis; positive MP antibody test; age under 12 y and normal liver and renal function were included in this study. Severe pneumonia; concomitant autoimmune diseases; concomitant other serious diseases; known allergy to the drugs used in this study; inability to cooperate with CT examination were excluded from this study. Prior approval from the ethics committee of our hospital was granted for this study, and informed consent was duly obtained from the parents or legal guardians of the participating patients. Scans were carried out utilizing a GE Optima CT660 64-slice spiral CT scanner for the CT examination. The patient assumed a supine position and was instructed to take a deep breath and hold it before the commencement of the scanning process. Parameters for the CT examination included a voltage of 100 kV, current ranging from 40 to 80 mA, and a slice thickness and interval of 5 mm. Scans were conducted from the lung apex to the diaphragm, allowing for the collection of specific information regarding lesion location, internal structure, morphology, density, and distribution. In cases where the child was uncooperative, chloral hydrate was administered for sedation. Following the examination, the obtained image information was analyzed by two skilled radiologists. In cases of discrepancy, a third senior radiologist was consulted to reach a consensus opinion. The children's ward upheld optimal air quality, humidity, and ventilation levels. Routine disinfection procedures were carried out, and patients were provided with essential treatments such as anti-infective therapy. Oral azithromycin powder (Pfizer Pharmaceuticals Ltd., Registration No: H10960112, 0.1 g/sachet) was administered to the control group. The treatment protocol involved a once-daily dosage for five consecutive days, with 10 mg/kg given on the 1st d, followed by 5 mg/kg from the 2nd-5th d. For the observation group, a combined therapeutic approach involving the usage of both azithromycin and ambroxol hydrochloride was implemented. The dosage of azithromycin corresponded with that employed in the control group, while ambroxol hydrochloride injection (Manufacturer: Sichuan Meidakanghua Pharmaceutical Co., Ltd., registered under H20193359, specification of 2 ml containing 15 mg) was administered intravenously. The administration of ambroxol hydrochloride entailed a dosage of 7.5 mg per dose, given twice daily for children aged 2 y-6 y, and 15 mg per dose, prescribed twice daily for children aged 7 y-12 y. The treatment cycle spanned 7 d, comprising a complete course of treatment. Clinical efficacy was evaluated according to the practical pediatrics guidelines by Wang *et al.*[12]: In cured; within 5 d of treatment, the patient experienced a complete recovery, with their body temperature returning to normal, a remarkable improvement in cough and sputum symptoms and the complete disappearance of lung rales. In marked effectiveness; within 5 d of treatment, noticeable progress was observed, including a gradual decrease in body temperature, alleviation of cough and sputum symptoms and mostly resolved lung rales. In effective; within 5 d of treatment, the patient

exhibited positive outcomes, such as a decrease in body temperature, relief from cough and sputum symptoms and reduced lung rales. In ineffective; within 5 d of treatment, the patient's body temperature did not decrease and symptoms did not improve. Overall treatment effective rate=Number of cured children+mumber of markedly effective children+number of effective children/total number of children in each group×100 % The comparison was made between the two groups of patients in terms of the time needed for temperature normalization, cessation of cough, and disappearance of lung rales. In CT signs, the comparison was made between the two groups of patients to evaluate the changes in different chest CT signs following a 7 d treatment period. The adverse reactions that manifested during the treatment period were recorded and subjected to a comparative analysis between the two groups of patients. Statistical Package for the Social Sciences (SPSS) 25.0 will be employed to perform the statistical analysis in this research. Continuous variables will be presented as means and standard deviations, and their analysis will be conducted using t-tests. Categorical variables, on the other hand, will be expressed as frequencies and percentages (n (%)) and assessed using Chi-square (χ^2) tests. To establish statistical significance, a threshold of $p<0.05$ will be utilized. With an overall treatment effective rate of 94.29 %, the observation group exhibited a notable increase in efficacy as opposed to the control group's rate of 77.14 % ($p<0.05$) as shown in Table 1. In comparison to the control group, the observation group exhibited a notable decrease in the time needed for temperature recovery, cough disappearance, and disappearance of lung rales ($p<0.05$) as shown in Table 2. There was no significant discrepancy in the positive number of various chest CT signs between the two groups before treatment ($p>0.05$). Subsequent to treatment, there was a substantial decrease in patients with ground-glass opacities within the control group. Conversely, the observation group displayed a marked reduction in patients with ground-glass opacities, lung consolidation, bronchial wall thickening, and lithotripsy sign ($p<0.05$). Moreover, the reduction in patients with ground-glass opacities and bronchial wall thickening was remarkably greater in the observation group as opposed to the control group ($p<0.05$) as shown in Table 3. No notable difference in the incidence of adverse reactions was found between the control group (17.14 %) and the observation group (20.00 %), ($p>0.05$) during the treatment period. Both groups of patients experienced adverse reactions, including rash, nausea/vomiting, and abdominal pain as shown in Table 4. In children, MPP is a frequently encountered respiratory infectious disease that manifests with symptoms including cough, fever, and wheezing. These symptoms can have a noticeable impact on a child's appetite and sleep[13]. Difficulty in detecting the early interstitial changes, which serve as the primary pathological manifestations of MPP, using conventional chest X-ray examinations can lead to delays in diagnosis and treatment. However, chest CT examinations provide a direct visualization that allows for the identification of lesion location, range, and lung tissue changes, including bronchial inflammation, interstitial pneumonia, and mixed lesions[14]. Apart from affecting the lung parenchyma, MPP in children can also result in adjacent structural changes, including bronchial wall thickening[15]. CT imaging, known for its high resolution and ability to adjust imaging densities, offers a clear visualization of lung lesions and tissue changes. When needed, contrast-enhanced scans can be employed to obtain clearer images, which overcome the limitations of overlapping images often encountered in X-ray examinations. This allows for the accurate identification of lesion location[16,17]. Evaluating the efficacy of ambroxol hydrochloride in conjunction with azithromycin in treating pediatric MPP and observing the changes in chest CT signs were the objectives of this study. Through the comparison of clinical efficacy, time to resolution of lung rales, time to temperature recovery, cough disappearance, and changes in chest CT signs between the observation group and the control group, it was determined that the treatment of MPP in children with the combination of ambroxol hydrochloride and azithromycin provided notable advantages. The observation group exhibited substantially shorter time to temperature recovery, cough disappearance, and resolution of lung rales compared to the control group ($p<0.05$). Furthermore, the overall treatment effective rate in the observation group was remarkably higher than that in the control group ($p<0.05$). Regarding the changes in chest CT signs, there was no notable difference in the prevalence of various positive signs between the two groups before treatment ($p>0.05$). However, after treatment, the number of patients with ground-glass opacities, lung consolidation, bronchial wall thickening, and cobblestone

appearance significantly decreased in both groups, with a greater reduction observed in the observation group ($p<0.05$). Adverse reactions, such as rash, nausea/vomiting, and abdominal pain, occurred in both groups, with no marked difference in the incidence between the observation and control groups ($p>0.05$). To conclude, the combined administration of ambroxol hydrochloride and azithromycin exhibited remarkable effectiveness in treating MPP in children. By adopting this treatment approach, there was a decrease in the duration of symptoms and an enhancement in the resolution of lung lesions, while the risk of adverse reactions remained unchanged. Nevertheless, this study is not without limitations, including a relatively small sample size and its restriction to a single hospital. To validate these findings, further multicenter studies with larger sample sizes are warranted. Moreover, forthcoming research endeavors can focus on investigating the mechanisms and long-term treatment effects of combined ambroxol hydrochloride and azithromycin therapy in MPP.

TABLE 1: CURATIVE EFFECT

Group (n=35)	Cured	Marked effective	Effective	Ineffectiveness	Overall effective rate
Observation	21 (60.00)	9 (25.71)	4 (19.05)	2 (5.71)	33 (94.29)
Control	12 (34.29)	8 (22.86)	7 (20.00)	8 (22.86)	27 (77.14)
χ^2					4.200
p					0.040

TABLE 2: SYMPTOM RESOLUTION TIME

Group (n=35)	Fever extinction time	Cough disappearance time	Time for lung rales to disappear
Observation	4.04±0.90	4.51±1.29	4.14±1.11
Control	5.40±1.04	5.42±1.32	5.08±1.24
t	6.772	5.060	4.084
p	0.000	0.000	0.000

TABLE 3: CT SIGNS

CT signs	Control (n=35)		χ^2	p	Observation (n=35)		χ^2	p
	Before	After			Before	After		
Ground-glass opacities	21 (60.00)	10 (28.57)	7.006	0.008	22 (62.86)	3 (8.57)*	22.462	0.000
Lung consolidation	13 (37.14)	7 (20.00)	2.52	0.112	12 (34.29)	2 (5.71)	8.929	0.003
Gas containing bronchial sign	7 (20.00)	4 (11.43)	0.971	0.324	8 (22.86)	3 (8.57)	2.696	0.101
Bronchial wall thickening	20 (57.14)	13 (28.57)	2.809	0.094	22 (62.86)	5 (14.29)*	17.425	0.000
Lithotripsy sign	9 (25.71)	5 (14.29)	1.429	0.232	9 (25.71)	2 (5.71)	5.285	0.022
Pleural effusion	5 (14.29)	3 (8.57)	0.565	0.452	4 (11.43)	2 (5.71)	0.729	0.393
Lymphadenopathy	4 (11.43)	2 (5.71)	0.728	0.393	5 (14.29)	1 (2.86)	2.917	0.088

Note: (*): Indicates that the positive proportion of the observation group after treatment was significantly lower than that of the control group after treatment

TABLE 4: ADVERSE REACTIONS n (%)

Group (n=35)	Rash	Nausea and vomiting	Celialgia	Overall incidence
Observation	3 (8.57)	1 (2.86)	3 (8.57)	7 (20.00)
Control	2 (5.71)	2 (5.71)	2 (5.71)	6 (17.14)
χ^2				0.094
p				0.759

Conflict of interests:

The authors declared no conflict of interests.

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