Efficacy of Terbutaline in Conjunction with Erythromycin in Managing *Mycoplasma pneumoniae* Bronchitis

YULONG TANG*

Department of Pediatrics, The Second Peoples' Hospital of Nantong, Nantong, Jiangsu Province 226002, China

Tang: Terbutaline and Erythromycin in *Mycoplasma pneumoniae* Bronchitis

This study seeks to assess the efficacy of terbutaline in conjunction with erythromycin in managing *Mycoplasma pneumoniae* bronchitis. Between September 2022 and August 2023, we chose 87 children diagnosed with *Mycoplasma pneumoniae* bronchitis, which were admitted to our hospital and subsequently split into an observation group consisting of 45 cases and a control group with 42 cases through random selection. Routine treatments, such as antitussives and antipyretics, were administered to both groups. Meanwhile, the control group was treated with intravenous erythromycin, and the observation group received terbutaline inhalation treatment as an adjunct. The evaluation of the clinical efficacy of both groups involved a scrutiny of various parameters, including the period of symptom resolution, inflammatory markers, immune function indicators, and lung function markers. Comparatively, the observation group exhibited a much higher efficacy, with a total effective rate of 91.11 %, in contrast to the control group (71.43 %, p<0.05). Subsequent to the treatment, the levels of inflammatory markers (high-sensitivity C-reactive protein, tumor necrosis factor-alpha and procalcitonin) in the observation group saw a substantial decline compared to pre-treatment levels, and were lower than those in the control group (p<0.05). For immune function indicators, the observation group displayed considerably higher cluster of differentiation 4^+ cell counts and cluster of differentiation 4^+/cluster of differentiation 8^+ ratios, as well as notably lower cluster of differentiation 8^+ cell counts in comparison to the control group (p<0.05). A reduced duration of symptom resolution and disappearance of lung sounds was found in the observation group as opposed to the control group. Furthermore, following the treatment, the lung function markers (forced expiratory volume 1/forced vital capacity %) demonstrated notable improvement in the observation group as opposed to the control group (p<0.05). Terbutaline in conjunction with erythromycin exhibits good efficacy in managing *Mycoplasma pneumoniae* bronchitis in children. This comprehensive treatment can considerably ameliorate symptoms, decrease inflammation, modulate immune function, and enhance lung function. As a result, it merits clinical endorsement.

Key words: Terbutaline, erythromycin, *Mycoplasma pneumoniae*, bronchitis, tracheobronchitis

Bronchitis has a heightened occurrence in infants, primarily attributable to elements such as cold climate, reduced immune function, bronchial spasms leading to ischemia, and exposure to air pollution and particulate matter, which render children more vulnerable to the condition[1,2]. The primary clinical manifestations of bronchitis encompass cough, sputum production, fever, abnormal lung auscultation, and wheezing.

Mycoplasma pneumoniae (*M. pneumoniae*) primarily impacts children and adolescents, serving as a prevalent pathogen that spreads *via* droplet transmission, causing *M. pneumoniae* or tracheobronchitis[3]. Bronchitis, frequently observed in children, is a respiratory infection distinguished by symptoms like nasal congestion, clear rhinorrhea, sore throat, and hoarseness. Failure to seek treatment may result in the progression to chronic bronchitis, leading to increased complexities in treatment, prolonged disease duration, and substantial impact on the life quality of affected children[4].

Erythromycin is presently widely employed in pediatric clinical environments to treat *M. pneumoniae* infection[5]. Nevertheless, the diminishing sensitivity of *M. pneumoniae* to the drug and the emergence of drug resistance have led to a gradual limitation in the effectiveness of erythromycin. Additional drug combinations are frequently required

*Address for correspondence
E-mail: xrzs20081010@163.com

to enhance treatment effectiveness. Terbutaline, a bronchodilator primarily composed of terbutaline sulfate, selectively stimulates Beta (β)-2 receptors in the airways. Its capacity to alleviate bronchial smooth muscles and restrain the release of inflammatory mediators makes it suitable for addressing diverse pulmonary ailments[6,7]. Nevertheless, there is insufficient research available on the utilization of terbutaline alongside erythromycin in addressing *M. pneumoniae* bronchitis.

As a result, this study seeks to observe the therapeutic efficacy of terbutaline in combination with erythromycin in managing *M. pneumoniae* bronchitis. It intends to explore the impact of this combination therapy on clinical symptoms and the microbiological outcomes, with the goal of providing more effective treatment options and clinical guidance.

MATERIALS AND METHODS

General information:

During the period spanning from September 2022 to August 2023, we chose 87 children diagnosed with *M. pneumoniae* bronchitis, who were admitted to our hospital and subsequently split into an observation group consisting of 45 cases and a control group with 42 cases through random selection. Comprising 25 males and 20 females, the observation group had an age range of 5 y-12 y, with an average age of (7.14±1.54) y, and average disease duration of (5.18±0.53) d. The control group included 22 males and 20 females, aged 5 y-13 y, with an average age of (7.34±1.36) y, and a disease duration ranging from 3 d-12 d, with an average of (5.36±0.66) d. No substantial distinctions were found in fundamental characteristics, such as age, gender, and disease period between the two groups (p>0.05), indicating their similarity.

Inclusion criteria: Children diagnosed with *M. pneumoniae* infection bronchitis through X-ray examination and pathogenic detection and aged between 5 and 13, and obtained informed consent from the guardian and signed an informed consent form.

Exclusion criteria: Patients with severe pneumonia; children with congenital digestive system diseases, genetic metabolic diseases, sepsis, congenital heart disease; patients with asthma, pulmonary tuberculosis, and significant organ diseases such as heart, brain, lung, liver, and kidney and individuals allergic or hypersensitive to the medications employed in this study.

Treatment methods:

Standard treatments including antitussives and antipyretics were administered to both groups. Furthermore, on the 1st d of hospitalization, the control group underwent a 5 d course of intravenous erythromycin administration (Hunan Kelun Pharmaceutical Co., Ltd., Batch No: H43020028) at a dosage of 10 mg/kg/d administered once daily. In conjunction with the control group's routine, the study group was administered additional terbutaline inhalation treatment. The terbutaline was amalgamated with 2 ml of normal saline to produce a final concentration of 5 mg/ml, and the resultant blend was inhaled twice a day for 15 min per session, over a 5 d period.

Observation indicators and evaluation criteria:

Clinical efficacy: An evaluation of the clinical efficacy between the two groups was undertaken. The criteria for efficacy determination were as follows; complete disappearance of clinical symptoms and normal imaging examination after treatment indicated cure; notable enhancement in clinical symptoms and imaging examinations approaching normalcy indicated marked improvement; partial improvement in clinical symptoms and imaging examination indicated improvement and failure to meet the above criteria after treatment indicated ineffectiveness.

Inflammatory markers and T lymphocyte subsets: A comparison of inflammatory markers and T lymphocyte subsets was undertaken in the two groups. Blood samples were drawn from both groups, with each sample amounting to 5 ml before and after treatment. The isolated serum was refrigerated and reserved for analysis, and the levels of highly sensitive Tumor Necrosis Factor-Alpha (TNF-α), Procalcitonin (PCT), and high sensitivity C-Reactive Protein (hs-CRP) were gauged *via* the Enzyme-Linked Immunosorbent Assay (ELISA). T lymphocyte subsets in both groups were assessed using flow cytometry, encompassing Cluster of Differentiation (CD) 8^+ and $CD4^+$, and calculating the $CD4^+/CD8^+$ ratio.

Symptom resolution time: The time to resolution of symptoms between the two groups was compared, encompassing the duration of cough and sputum

disappearance, defervescence, and the clearance of lung sounds.

Lung function: Comparative measurement of lung function in both groups was conducted before and after treatment. This included the assessment of the Forced Expiratory Volume 1 (FEV_1) and the FEV_1/Forced Vital Capacity (FVC) using a spirometer. A higher value signified superior lung function.

Statistical analysis:

Utilizing the Statistical Package for the Social Sciences (SPSS) 25.0 statistical software, the analysis was performed. By utilizing an independent sample t-test, a comparison between the two groups was performed using the measurement data presented as mean±standard deviation. Utilizing the Chi-square (χ^2) test, the count data were analyzed. The criteria for establishing statistical significance were defined at a level of $p<0.05$.

RESULTS AND DISCUSSION

Following treatment, the observation group exhibited a total effective rate of 91.11 %, notably surpassing the 71.43 % in the control group, signifying a notable difference ($p<0.05$), as indicated in Table 1.

At the outset of the treatment, no notable disparities in the levels of hs-CRP, PCT, and TNF-α between the two groups was observed ($p>0.05$). Yet, post-treatment, the levels of hs-CRP, PCT, and TNF-α substantially decreased in both groups compared to pre-treatment levels, and the observation group demonstrated lower levels than the control group, documenting a remarkable difference ($p<0.05$) as shown in Table 2.

Prior to treatment, no marked discrepancies in the levels of CD4+, CD8+, and CD4+/CD8+ was identified between the two groups ($p>0.05$). Subsequent to treatment, there was an enhancement in the immune function of both groups, with elevated CD4+ and CD4+/CD8+ levels, as well as reduced CD8+ levels in the observation group relative to the control group, demonstrating a notable difference ($p<0.05$), as indicated in Table 3.

The observation group exhibited earlier times for defervescence (2.64±0.57), resolution of cough (4.56±1.10), and disappearance of lung sounds (4.04±0.82) compared to the control group (3.24±0.73, 5.36±1.01, and 5.26±0.89 respectively), indicating a remarkable difference ($p<0.05$) as shown in fig. 1.

No notable differences in FEV_1 and FEV_1/FVC % between the two groups was found prior to treatment ($p>0.05$). Subsequently, following treatment, there was an increase in both FEV_1 and FEV_1/FVC % in both groups, with the observation group demonstrating a higher level of improvement as opposed to the control group ($p<0.05$) as shown in Table 4.

TABLE 1: CURATIVE EFFECT

Group (n)	Cured	Marked improvement	Improvement	Ineffectiveness	Overall effective rate
Observation (45)	11 (24.44)	16 (35.56)	14 (31.11)	4 (8.89)	41 (91.11)
Control (42)	8 (19.05)	14 (33.33)	8 (19.05)	12 (28.57)	30 (71.43)
χ^2					5.607
p					0.018

TABLE 2: INFLAMMATORY CYTOKINE LEVELS

Group (n)	hs-CRP (mg/l)		PCT (ng/ml)		TNF-α (pg/ml)	
	Before	After	Before	After	Before	After
Observation (45)	7.57±0.39	1.91±0.15*	8.30±0.43	0.39±0.13*	10.36±0.60	5.49±0.37*
Control (42)	7.41±0.45	3.47±0.34*	8.26±0.65	1.85±0.23*	10.47±0.58	8.15±0.50*
t	-1.732	16.397	-0.303	36.484	0.843	28.254
p	0.087	0.000	0.763	0.000	0.402	0.000

Note: (*): Indicates noteworthy difference following treatment compared with prior to treatment

TABLE 3: T LYMPHOCYTE SUBSETS

Group (n)	CD4+ (%)		CD8+ (%)		CD4+/CD8+	
	Before	After	Before	After	Before	After
Observation (45)	47.76±3.39	41.11±4.78	21.82±5.33	26.81±4.00	2.38±0.63	1.51±0.27
Control (42)	46.80±3.42	44.17±4.12	21.85±4.84	23.41±3.32	2.33±0.51	1.88±0.36
t	-1.308	3.188	-0.026	-4.309	-0.392	5.584
p	0.194	0.002	0.979	0.000	0.696	0.000

Note: (*): Indicates noteworthy difference following treatment compared with prior to treatment
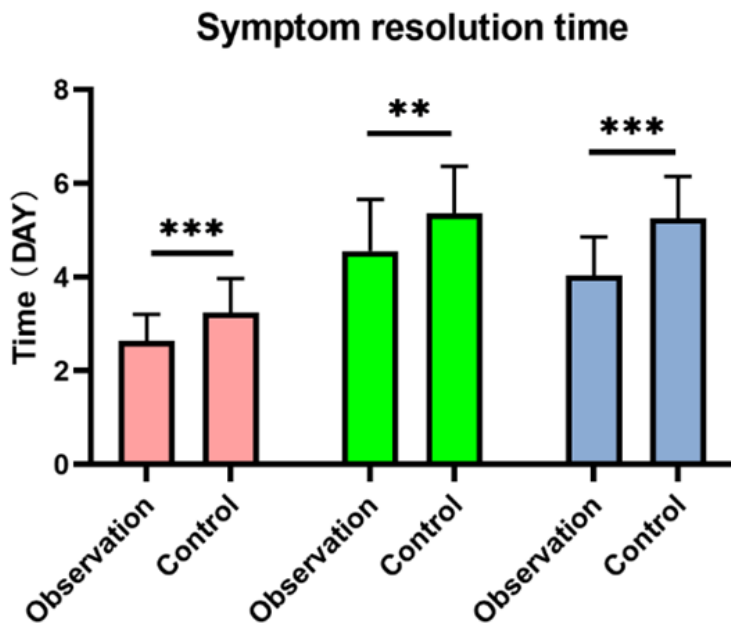

Fig. 1: Symptom resolution time
Note: **$p < 0.01$, ***$p < 0.001$, (█): Fever extinction time; (█): Cough disappearance time and (█): Time for lung rales to disappear

TABLE 4: PULMONARY FUNCTION INDEX

Group (n)	FEV_1 (L)		FEV_1/FVC	
	Before	After	Before	After
Observation (45)	1.52±0.29	2.16±0.48*	34.98±7.60	51.20±11.62*
Control (42)	1.40±0.35	1.83±0.42*	34.26±8.21	39.09±13.19*
t	-1.731	-3.372	-0.424	-4.552
p	0.087	0.001	0.672	0.000

Note: (*): Indicates noteworthy difference after treatment compared with before treatment

Airway hyper responsiveness, a pathophysiological change present in bronchitis, is associated with type III hypersensitivity reactions and T-cell mediated immune responses[8]. Currently, the primary strategy for managing this condition in clinical practice is comprehensive treatment. Addressing acute bronchitis in children involves key interventions such as antibacterial, anti-inflammatory, expectorant, and cough suppressant methods, along with improving lung ventilation. Erythromycin contributes significantly to the treatment of bronchitis by virtue of its diverse mechanisms of action, which involve anti-inflammatory, bronchodilatory, and immunoregulatory effects[9,10]. Terbutaline, a stable selective α2 adrenergic receptor agonist, works by binding to α2 adrenergic receptors, thereby elevating cellular cyclic adenosine monophosphate levels. As a result, it effectively relaxes bronchial

smooth muscles, clears secretions in the trachea and bronchi, and relieves bronchospasm. As a result, it is frequently utilized in the treatment of bronchial asthma, bronchitis, and cough-variant asthma[11]. The study was conducted to look into the therapeutic efficacy of combining terbutaline with erythromycin for the treatment of *M. pneumoniae* bronchitis, and to carry out comparative analysis of clinical efficacy, inflammatory markers and T lymphocyte subgroups, as well as the resolution time of symptoms and lung function in the two groups of children.

At the outset, the findings brought to light that the total effective rate in the observation group (91.11 %) was substantially higher than in the control group (71.43 %), indicating a notable difference. This implies that the combination of terbutaline with erythromycin in treating *M. pneumoniae* bronchitis is remarkably more effective than treatment with erythromycin alone. This aligns with previous research, signifying the favorable impact of terbutaline, a bronchodilator, in effectively relaxing bronchial smooth muscles and reducing airway resistance, thereby alleviating symptoms in children[12].

Following an infection, there is a marked rise in the serum levels of hs-CRP, PCT, and TNF-α, which can be employed as evaluation markers for appraising the treatment of acute bronchitis[13]. The study assessed and compared the levels of inflammatory markers and T lymphocyte subgroups. The findings indicated that prior to treatment; no notable distinctions existed in the levels of inflammatory markers (hs-CRP, PCT, and TNF-α) between the two groups. Nevertheless, subsequent to the treatment, the levels of these inflammatory markers were notably lower in the observation group compared to pre-treatment levels, and were inferior to those in the control group, with a remarkable difference. This suggests that the combined treatment of terbutaline with erythromycin effectively suppresses the inflammatory response, leading to an improved relief of inflammatory symptoms.

T-lymphocyte subsets are instrumental in modulating immune function, wherein $CD4^+$ and $CD8^+$ are classifications of T lymphocytes. $CD4^+$ fosters antibody production and the differentiation of B lymphocytes, thereby diminishing the body's immune response, while $CD8^+$ exerts a cytotoxic impact on antigen-expressing target cells, and is vital in combating viral infections, acutely rejecting allogeneic transplants, and eradicating tumor cells. It assists the body in removing pathogens, and thus,

the ratio of the levels of the two subsets objectively mirrors the body's immune function[14,15]. In this study, the combined treatment with terbutaline and erythromycin enhanced the immune function of children. The observation group exhibited remarkably higher levels of $CD4^+$ and $CD4^+/CD8^+$, with a notably lower level of $CD8^+$ compared to the control group, demonstrating a notable distinction. Symptom improvement and resolution occurred earlier in the observation group than in the control group, and there was also a marked improvement in lung function markers (FEV_1, FEV_1/FVC %). FEV_1 and FEV_1/FVC % directly indicate children's respiratory function[16]. This further underscores the effectiveness of terbutaline combined with erythromycin in managing *M. pneumoniae* bronchitis, as it effectively relieves inflammatory symptoms and improves immune and lung function.

In summary, the combined administration of terbutaline with erythromycin proves to be significantly effective in managing bronchitis caused by *M. pneumoniae*. Not only does this combined treatment effectively alleviate inflammatory symptoms, but it also improves immune function and lung function. Nonetheless, even with the clinical importance of this study's findings, there remains a need for additional large-scale, multi-center studies to validate its effectiveness and safety. This will further enhance treatment strategies and furnish vital guidance to clinicians in the management of bronchitis caused by *M. pneumoniae*.

Conflict of interests:

The authors declared no conflict of interests.

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