Analysis of Clinical Efficacy of Erythromycin Combined with Oseltamivir Phosphate Granules in the Treatment of Mycoplasma Pneumonia in Children

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We attempt to discuss the improvement of clinical efficacy of erythromycin combined with oseltamivir phosphate granules in children with mycoplasma pneumonia and its influence on lung function and infection indicators. We selected 60 patients with mycoplasma pneumonia in children from February 2019 to June 2020 and randomly divided them into observation group (30 cases of erythromycin combined with oseltamivir phosphate granules) and control group (oseltamivir phosphate) Wei granule treatment (30 cases), compare the clinical effective rate, changes in various indicators of lung function, disappearance time of clinical symptoms and changes in serum procalcitonin, C-reactive protein and interleukin 6 concentration levels in both groups before and after treatment. Observation group possessed remarkably higher ratio of time to peak tidal expiratory flow to total expiratory time, ratio of instantaneous velocity to tidal peak expiratory velocity at 75 % tidal volume and tidal volume than control group ($p<0.05$); and it had remarkably lower antipyretic time, rales disappearance time, throat and tonsil hyperemia disappearance time than control group ($p<0.05$); observation group possessed remarkably lower length of stay than control group ($p<0.05$) and procalcitonin, interleukin 6 and C-reactive protein concentration in serum of observation group declined more than control group ($p<0.05$). The total clinical effective rate of observation group (93.4 %) was remarkably higher than control group (80 %) ($p<0.05$). Erythromycin combined with oseltamivir phosphate particles can remarkably improve the clinical effectiveness of mycoplasma pneumonia in children, improve lung signs and clinical effectiveness and reduce procalcitonin, C-reactive protein and interleukin 6 concentration in serum. Effective treatment of pneumonia provides clinical guidance value.

Key words: Erythromycin, oseltamivir phosphate granules, mycoplasma pneumonia, clinical efficacy

Pneumonia is one most common serious infections in childhood and ranks top three causes of pediatric hospitalization in the United States every year[1]. *Mycoplasma pneumoniae* Pneumonia (MPP) caused by *Mycoplasma pneumoniae* (MP) infection is the commonest condition of Community-Acquired Pneumonia (CAP) in children[2]. Although MP infection is generally considered to be a self-limiting disease, but sometimes it might cause all sorts of serious complications; for example, arthritis and necrotizing pneumonia[3]. However, there are still some cases that still show clinical and radiographic deterioration after 7 d or more of macrolide antibiotic treatment, which is defined as Refractory MPP (RMPP)[4]. The etiology of RMPP has multiple causes, including macrolide resistance, other pathogens infection and immune disorders[4,5]. Contrast Non-RMPP (NRMPP) cases, RMPP cases display frequent cough, fever and abnormal pulmonary signs and pneumonia progresses to life-threatening pneumonia[6]. Therefore, early and accurate diagnosis of RMPP is particularly important for pediatricians to treat and prevent disease progression[7]. Macrolides (erythromycin) are widely used as anti-infective treatments for childhood pneumonia, mainly antibiotics for infections caused by gram-positive bacteria[8]. Oseltamivir is the drug of choice for treating patients with influenza virus infection[9]. Therefore, our study attempts to discuss the effect of erythromycin combined with oseltamivir phosphate granules on the clinical efficacy of children with mycoplasma pneumonia. We selected 60 patients with mycoplasma pneumonia in children from February

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2019 to June 2020 as participants. Patients met the standard of "Guidelines for diagnosis and treatment of CAP in children (2019 version)"[10] and are diagnosed with childhood pneumonia after clinical examination; children without communication or mental disorders; children without systemic immune system diseases. Children with disease damage to important organs such as liver and kidney; patients with cardiovascular disease; patients with unstable vital signs; patients with known malignancy; children with other chronic respiratory diseases; children allergic to erythromycin or oseltamivir phosphate. This study had got approval from the ethics committee of our hospital. We divided patients into control group and observation group (n=30). 21 males and 19 females included in control group, ages were from 3 y to 12 y old and average was about (6.58±3.04) y old. 16 males and 24 females included in control group, ages were from 3 y to 12 y old and averages were about (6.22±3.64) y old. The general data of both groups are comparable ($p>0.05$). After admission, both groups received routine treatment, including resolving phlegm, relieving cough, volume expansion, maintaining homeostasis of internal environment, oxygen inhalation and mechanical ventilation when necessary, routine anti-infection, nurses routinely carried out mechanical ventilation nursing, airway management, condition monitoring and nutritional support and so on, closely monitor the vital signs and respiratory function of each patient and find complications such as respiratory failure as early as possible. Control group adopted oseltamivir phosphate granules, 30 mg, taken orally twice a day; after receiving the same therapy as control group, observation group received erythromycin injection (Shanghai Bohu Biotechnology Co., Ltd. NMPN: H24580467), 30 mg/kg/d, 2 intravenous infusions. After 1 w treatment, evaluated relevant clinical indicators. Observed and recorded the fever clearance time, rales disappearance time, throat and tonsil congestion clearance time and hospitalization time of both groups after treatment. Collect 5 ml of fasting elbow vein of patients in both groups in the morning of the 2 d of admission and put it into two centrifuge tubes, 3 ml for each. Left standing one tube at room temperature for 30 min, centrifuged in a 3500 r/min centrifuge (4°) for 10 min, extracted the supernatant, adopted enzyme linked immunosorbent assay to exam C-Reactive Protein (CRP), Procalcitonin (PCT) and Interleukin 6 (IL-6) concentration levels. After 3 d and 7 d treatment, detected CRP, PCT and IL-6 concentration levels in the serum. Monitored the pulmonary function of both groups before and after treatment. The main monitoring indexes were: Tidal volume, peak time ratio, instantaneous velocity ratio to tidal peak expiratory velocity at 75 % tidal volume, mid inspiratory velocity ratio to mid expiratory velocity ratio, the monitoring instrument is a pulmonary function monitor (purchased from JEAGER, Germany). In 2019, the National Health Commission and the State Bureau of Traditional Chinese Medicine organized experts from various related disciplines to jointly issue the "Guidelines for diagnosis and treatment of CAP in children (2019 version)" as the criterion for efficacy determination, evaluated the clinical efficacy according to four indexes like symptoms, signs, laboratory examination and etiology. Significantly effective patient's condition improved significantly and the four indexes recovered completely or one of them did not recover completely; effective condition improved after treatment and 2-4 of the four indexes still did not fully recover and invalid condition has not improved significantly after 3 d treatment, even pulmonary signs worsen.

Total clinical effective rate=(Significantly effective+Effective)/Total cases

Use Statistical Package for Social Sciences (SPSS) 22.0 software to analyze all data. Express the count data as n %, comparison of both groups tested by χ^2. Measurement data (pulmonary function, clinical symptoms, CRP, PCT and IL-6 concentration levels in the serum, etc.) conforms to normal distribution and homogeneity of variance as ($\bar{x}\pm s$). Use t test for comparison between groups. $p<0.05$ indicated the differences possessed statistical significance. Before treatment, compare both groups on Mean Tidal Inspiratory Flow/Mean Tidal Expiratory Flow (MTIF/MTEF), Tidal Volume (V-T), ratio of time to Peak Tidal Expiratory Flow/Total Expiratory Time (t-PTEF/t-E %) and ratio of Instantaneous Velocity to Tidal Peak Expiratory Velocity at 75 % Tidal Volume value (TEF25/PTEF %) the differences possessed no statistical significance ($p>0.05$); after treatment, observation group possessed remarkably higher t-PTEF/t-E %, TEF25/PTEF and V-T than control group, so it was of statistical significance ($p<0.05$) as shown in Table 1. Observation group possessed remarkably lower antipyretic time, rales disappearance time, throat and tonsil congestion disappearance time and hospitalization time than

control group, it had statistical significance ($p<0.05$); after receiving erythromycin combined with oseltamivir phosphate granules treatment, hospitalization time shortened remarkably, it had statistical significance ($p<0.05$) as shown in Table 2. Before treatment, PCT, IL-6 and CRP levels of both groups had no difference, so it had no statistical significance ($p>0.05$); after treatment, compared PCT, IL-6, CRP levels of both groups, observation group had bigger downtrend than control group, they were remarkably different, so it possessed statistical significance ($p<0.05$) as shown in Table 3. After both receiving 1 w treatment, there were 28 cases significantly effective and effective in observation group, so the total clinical effective rate was (93.3 %); there were 24 cases significantly effective and effective in control group, so the total clinical effective rate was (80 %), clinical efficacy had statistical significance ($p<0.05$) as shown in Table 4. *Mycoplasma* is a common pathogen causing CAP in children. Studies have shown that childhood pneumonia caused by MP accounts for between 20 % and 40 % of all childhood pneumonia[11]. MP infection rates may increase with age. In the early stages of the disease, it is hard to detect MP-Immunoglobulin M (MP-IgM)[12]. After children infected MP, stimulates the infiltration of inflammatory cells and inflammatory factors release, after alveolar inflammatory cells infiltration, it can lead to necrosis of tracheal mucosa and even blockage of small airways, immune disorder caused by MP infection is also a main factor in the pathogenesis of RMPP[13]. It has been reported that the invasion of aflatoxin damaged mouse lung tissue, accompanied by increased pro-inflammatory cytokines expressions (such as Tumour Necrosis Factor Alpha (TNF-α) and IL-6) and immune disorders. This suggests a potential link between aflatoxin and cytokines and their pathogenic role in MPP[14]. We conducted the study to discuss that the clinical efficacy has relationship with cytokines. Erythromycin combined with oseltamivir phosphate granules can remarkably improve the clinical efficacy and reduce the infection indexes (IL-6 and CRP) in children with mycoplasma pneumonia, which is consistent with the results of former studies. Macrolide antibiotics are the preferred antibiotics for children with MP infection. Macrolides can affect the 50 s subunit of the ribosome of *Mycoplasma* cells, inhibit messenger Ribonucleic Acid (mRNA) transfer and protein synthesis and play a good antibacterial effect[15]. Clinically, erythromycin, as the first choice of macrolides, can maintain a high concentration in serum, so as to completely control mycoplasma pneumonia [16], some studies have found that macrolide antibiotics have significant effect on improving the clinical efficacy of patients with MPP. Moreover, some studies have reported that macrolide resistant children have less inhibitory effect on microorganisms and may not achieve the effect of treating MPP[17]. Since Japan first reported macrolide resistance 1970, the global prevalence of macrolide resistant MP has increased to 10 %-30 %, which will eventually lead to severe refractory MP[18]. If erythromycin is used for a long time, it will cause gastrointestinal dynamic changes, liver function damage and drug febrile reaction, so it has great side effects[19]. Oseltamivir in the treatment of respiratory tract infections has remarkably reduced adverse effects in children-related populations, for example, reducing the risk of otitis media and its complications[20]. The results showed that erythromycin combined with oseltamivir phosphate granules could remarkably improve the clinical efficacy of patients, but this study also has shortcomings. First of all, the sample size of the study is small, which will lead to biased results. Secondly, the comparison of adverse reactions was not included in this study, which needs to be further improved in future research. This study proved that the combination of erythromycin and oseltamivir phosphate particles can remarkably improve the clinical effectiveness of mycoplasma pneumonia in children, after treatment, observation group possessed remarkably higher t-PTEF/t-E %,TEF25/PTEF and V-T than control group, so it had statistical significance ($p<0.05$); observation group possessed remarkably lower antipyretic time, rales disappearance time, throat and tonsil congestion disappearance time than control group, it had statistical significance ($p<0.05$); observation group possessed remarkably lower hospitalization time than control group, it had statistical significance ($p<0.05$); observation group possessed bigger downtrend of PCT, IL-6 and CRP levels in serum than control group, they were remarkably different, so it possessed statistical significance ($p<0.05$); the total clinical effective rate of observation group (93.4 %) was remarkably higher compared with control group (80 %), it possessed statistical significance ($p<0.05$). Erythromycin combined with oseltamivir phosphate particles can remarkably improve the clinical effectiveness of mycoplasma pneumonia in children, improve the lung signs and clinical effectiveness and reduce PCT, CRP and IL-6 concentration in serum, it can provide clinical guiding value for the effective treatment of severe pneumonia.

TABLE 1: COMPARISON OF PULMONARY FUNCTION INDEXES BEFORE AND AFTER TREATMENT

Item	Before and after treatment	Observation group (n=30)	Control group (n=30)	t value	p value
V-T/kg (ml/kg)	Before treatment	8.52±1.38	8.52±1.38	0.36	0.75
	After treatment	11.79±2.06	9.94±1.41	8.26	0.001
t-PTEF/t-E (%)	Before treatment	38.14±8.31	39.59±10.27	0.25	0.79
	After treatment	46.79±6.06	41.94±5.41	7.05	0.001
TEF25/PTEF (%)	Before treatment	0.652±0.076	0.656±0.081	0.46	0.52
	After treatment	0.806±0.092	0.705±0.089	6.19	0.001
MTIF/MTEF	Before treatment	1.31±0.16	1.30±0.15	0.47	0.67
	After treatment	1.26±0.13	1.25±0.14	3.68	0.003

TABLE 2: COMPARISON OF CLINICAL SYMPTOMS DISAPPEARANCE AND HOSPITALIZATION TIME BETWEEN BOTH GROUPS

Item	Antipyretic time	Rale disappearance time	Throat and tonsil congestion disappearance time	Hospitalization time
Observation group	4.08±0.57	5.68±0.82	4.22±0.85	8.57±1.29
Control group	5.34±1.18	7.34±0.88	7.01±0.94	11.71±1.67
χ^2	5.13	3.71	7.31	4.03
p value	0.005	0.007	0.001	0.009

TABLE 3: COMPARISON OF PCT, IL-6, CRP BETWEEN BOTH GROUPS BEFORE AND AFTER TREATMENT

Group	Cases	PCT (μg/l)		IL-6 (pg/ml)		CRP (mg/l)	
		0.001		0.001		0.001	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	35	16.03±6.94	9.63±3.37	227.64±70.04	76.6±24.4	89.09±33.60	53.31±16.4
Control group	35	17.44±6.66	13.6±4.46	226.54±91.69	93.6±36.6	87.64±37.07	67.7±23.4
t value		0.41	4.56	0.15	2.24	0.07	3.91
p value		0.72	0.006	0.89	0.002	0.91	0.001

TABLE 4: COMPARISON OF CLINICAL EFFICACY AFTER TREATMENT

	Significantly effective	Effective	Invalid	Total clinical effective rate
Observation group	23 (76.67 %)	5 (16.67 %)	2 (6.7 %)	28 (93.3 %)
Control group	20 (66.67 %)	4 (13.3 %)	6 (20 %)	25 (80 %)
χ^2				5.67
p				0.005

Conflict of interests:

The authors declared no conflict of interest.

REFERENCES

1. Yan C, Yang H, Sun H, Zhao H, Feng Y, Xue G, *et al.* Diversity in genotype distribution of *Mycoplasma pneumoniae* obtained from children and adults. Jpn J Infect Dis 2020;73(1):14-8.
2. Pittet LF, Bertelli C, Scherz V, Rochat I, Mardegan C, Brouillet R, *et al.* Chlamydia pneumoniae and *Mycoplasma pneumoniae* in children with cystic fibrosis: Impact on bacterial respiratory microbiota diversity. Pathog Dis 2021;79(1):74-6.
3. Sauteur PM, van Rossum AM, Vink C. *Mycoplasma pneumoniae* in children: Carriage, pathogenesis and antibiotic resistance. Curr Opin Infect Dis 2014;27(3):220-7.
4. Medjo B, Atanaskovic-Markovic M, Radic S, Nikolic D, Lukac M, Djukic S. *Mycoplasma pneumoniae* as a causative agent of community-acquired pneumonia in children: Clinical features and laboratory diagnosis. Ital J Pediatr 2014;40(1):1-7.
5. Lee H, Yun KW, Lee HJ, Choi EH. Antimicrobial therapy of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children. Expert Rev Anti Infect Ther 2018;16(1):23-34.
6. Kutty PK, Jain S, Taylor TH, Bramley AM, Diaz MH, Ampofo K, *et al. Mycoplasma pneumoniae* among children hospitalized with community-acquired pneumonia. Clin Infect Dis 2019;68(1):5-12.
7. Dou HW, Tian XJ, Li Xin D, Ran WE, Wei ZH, Hong WA, *et al. Mycoplasma pneumoniae* macrolide resistance and MLVA typing in children in Beijing, China, in 2016: Is it relevant. Biomed Environ Sci 2020;33(12):916-24.
8. Kumar S, Roy RD, Sethi GR, Saigal SR. *Mycoplasma pneumoniae* infection and asthma in children. Trop Doct 2019;49(2):117-9.
9. Kumar S. *Mycoplasma pneumoniae*: A significant but underrated pathogen in paediatric community-acquired lower respiratory tract infections. Indian J Med Res 2018;147(1):23.
10. National Health Commission of the People's Republic of China, State Administration of Traditional Chinese Medicine. Guidelines for diagnosis and treatment of community-acquired pneumonia in children (2019 version). Chin J Clin Infect Dis 2019;12(1):6-13.
11. Chen P, Huang Z, Chen L, Zhuang S, Lin H, Xie J, *et al.* The relationships between lncRNA NNT-AS1, CRP, PCT and their interactions and the refractory *Mycoplasma pneumoniae* pneumonia in children. Sci Rep 2021;11(1):1-8.
12. Chen Y, Tian WM, Chen Q, Zhao HY, Huang P, Lin ZQ, *et al.* Clinical features and treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children. Zhongguo Dang Dai Er Ke Za Zhi 2018;20(8):629-34.
13. Kumar S, Garg IB, Sethi GR. Serological and molecular detection of *Mycoplasma pneumoniae* in children with community-acquired lower respiratory tract infections. Diagn Microbiol Infect Dis 2019;95(1):5-9.
14. Long TW, Lin JL, Dai JH. Influencing factors for the clinical effect of bronchoalveolar lavage in children with *Mycoplasma pneumoniae* pneumonia and atelectasis. Zhongguo Dang Dai Er Ke Za Zhi 2020;22(9):984-9.
15. Lu CY, Yen TY, Chang LY, Liau YJ, Liu HH, Huang LM. Multiple-locus variable-number tandem-repeat analysis (MLVA) of macrolide-susceptible and-resistant *Mycoplasma pneumoniae* in children in Taiwan. J Formos Med Assoc 2020;119(10):1539-45.
16. Xu XC, Dai K. Comparative observation of erythromycin and azithromycin in children with pneumonia and their effect on immunity. Chin J Clin 2018;46(2):235-7.
17. Zhao F, Guan X, Li J, Liu L, Gong J, He L, *et al.* Real-time PCR and quantitative culture for *Mycoplasma pneumoniae* load in pharyngeal swabs from children at preliminary diagnosis and discharge. Biomed Res Int 2020;2020.
18. Wood PR, Kampschmidt JC, Dube PH, Cagle MP, Chaparro P, Ketchum NS, *et al. Mycoplasma pneumoniae* and health outcomes in children with asthma. Anna Allergy Asthma Immunol 2017;119(2):146-52.
19. Zhang YM, Tan RH, Zhu P. Azithromycin combined with erythromycin in the treatment of pediatric mycoplasma pneumonia: A meta-analysis of randomized controlled trails. Chin J Antibiot 2018;43(2):238-48.
20. Zhou Y, Wang J, Chen W, Shen N, Tao Y, Zhao R, *et al.* Impact of viral coinfection and macrolide-resistant mycoplasma infection in children with refractory *Mycoplasma pneumoniae* pneumonia. BMC Infect Dis 2020;20(1):1-10.

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