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Original Research Article

Efficacy of roxithromycin with gamma globulin in children with mycoplasma pneumonia and its effect on immunity

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Abstract

Purpose: *To determine the efficacy of roxithromycin plus gamma globulin in the treatment of children with mycoplasma pneumonia (MPP) and its effect on immune function.*
Methods: *From January 2019 to January 2021, 100 children with MPP assessed for eligibility in Qingdao Women and Children's Hospital, Shandong Province, China, were recruited and randomized (1:1) to receive either gamma globulin (control group) or roxithromycin plus gamma globulin (study group). Levels of tumor necrosis factor (TNF)-α, immunoglobulin (Ig)A, IgM, and IgG were evaluated. Clinical indices, including fever reduction, cough disappearance, duration of hospital stay, etc were also assessed.*
Results: *The study group had a significantly higher clinical efficacy (88 %) than the control group (68 %) ($p < 0.05$). After treatment, patients in the study group showed lower levels of tumor necrosis factor (TNF)-α than those in the control group ($p < 0.05$). The eligible patients given roxithromycin plus gamma globulin showed significantly higher levels of immunoglobulin (Ig)A, IgM, and IgG versus those given gamma globulin alone ($p < 0.05$). Patients in the study group had a shorter time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay than those in the control group ($p < 0.05$).*
Conclusion: *Roxithromycin plus gamma globulin demonstrate significant benefits in the treatment of children with MPP by mitigating inflammatory response, enhancing immune function, and also significantly alleviating clinical symptoms. Thus, the combination treatment shows good potentials for use in clinical practice.*

Keywords: *Roxithromycin, Gamma globulin, Mycoplasma pneumonia, Immune function*

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INTRODUCTION

Mycoplasma pneumonia (MPP) is triggered by Mycoplasma (MP) infection and is a frequent respiratory tract infection in children [1]. Studies have shown that MPP accounts for about one-fifth of all pneumonia cases in children and is characterized by acute onset and severe illness, with manifestations such as fever, cough, and expectoration. Delayed treatment may lead to various adverse events, which compromises the quality of life of children. Therefore, there exists

an urgent need to provide early diagnosis and treatment for children with MPP [2,3]. It has been reported that MPP is potentially associated with serious complications in multiple systems and a prolonged course of disease [4]. The current treatment of MPP in children primarily centers on the prevention of infection. Roxithromycin is a semi-synthetic macrolide antibiotic that exhibits gastric acid resistance, high bioavailability, and good tissue permeability, as well as favorable effects on inhibition of bacterial protein synthesis [5-7]. Roxithromycin blocks protein synthesis in pathogenic microorganisms, and its intracellular concentration kills MPP [8]. Gamma globulin is an immunomodulator that yields enhanced anti-bacterial and anti-viral effects in combination with antibiotics. The present study was undertaken to investigate the efficacy of roxithromycin plus gamma globulin in the treatment of children with MPP and its impact on immune function.

METHODS

Ethical statement

This study was approved by the Ethics Committee of Qingdao Women and Children's Hospital, Shandong Province, China (no. 20180978). The patients and their families were informed of the purpose and procedures of the study, and they signed informed consent forms. The study protocol was conducted in accordance with the Declaration of Helsinki [9].

General information on patients

From January 2019 to January 2021, 100 children with MPP in Qingdao Women and Children's Hospital, Shandong Province, China were assessed for eligibility and were recruited and randomized (1:1) to either a control group or study group. The clinical characteristics of the control group (23 males and 27 females), were aged 2 - 11 years, with a mean age of 6.12 ± 2.24 years, course of disease of 5 - 12 days, and a mean course of 7.86 ± 3.25 days. These were comparable with those of the study group (24 males and 26 females), aged 2 - 10 years, with a mean age of 6.14 ± 2.20 years, course of disease of 5 - 11 days, and a mean course of 9.21 ± 3.46 days ($p > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria

Patients who met the diagnostic criteria for MPP, with complete clinical data and no allergies to the drugs used were included in this study.

Exclusion criteria

Patients who had other lung or systemic infections or non-mycoplasma pneumonia; with bronchial asthma and bronchiectasis; with major organ lesions and psychological disorders; with use of other drugs before the study, were excluded.

Treatment

Patients in both groups received comprehensive treatments involving anti-pyretic, anti-tussive, anti-asthmatic, and expectorant medications. The vital signs of the children were monitored. The control group received gamma globulin (Shanxi Kangbao Biological Products Co. Ltd; SFDA approval no. S19994004), at doses of 0.05 - 0.15 mL/kg daily for children under 5 years old, and 6 mL daily for children over 6 years old. The duration of treatment was 5 days. A similar administration regimen of gamma globulin was introduced to the patients in the study group.

The study group additionally received 5 mg/kg roxithromycin (Shanghai Xinyi Pharmaceutical Co. Ltd., SFDA approval no. H20023241), twice daily, and the duration of treatment was 5 days.

Determination of treatment indices

Clinical effectiveness

Cured: Sputum MPP was negative (-ve), the clinical symptoms disappeared, and chest X-rays showed no lung shadows or normal lung images. Markedly effective: Sputum MPP was negative (-ve), clinical symptoms basically disappeared, and chest X-ray showed a reduction of ≥ 95 % in lung shadow. Effective: Sputum MPP was negative (+ve), with alleviation in clinical symptoms, and chest X-ray showed a reduction of ≥ 80 % in lung shadow. Ineffective: Sputum MPP was negative (+ve), and clinical symptoms showed no substantial reductions or even worsened. The total treatment effectiveness (TE) was calculated as shown in Eq 1.

$$TE\ (\%) = (\sum Cc + Ec)/\ Tc \times 100 \ldots\ldots. (1)$$

where Cc = cured cases, Ec = effective cases and Tc = total cases

Immune function

Changes in levels of immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) in the two groups of children before and after treatment were determined.

Levels of inflammatory mediators

Changes in levels of serum tumor necrosis factor (TNF-α), interleukin-8 (IL-8), serum high-sensitivity C-reactive protein (CRP), and serum procalcitonin (PCT) in the two groups of children were determined using appropriate ELISA kits. 4 mL of fasting peripheral venous blood was collected before and after treatment. The blood samples were centrifuged at 3000 rpm, and levels of these parameters were determined using the ELISA kits provided by Beijing Biochemical Technology Co. Ltd., strictly in line with the kit instructions.

Time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay

The time elapsed to achieve mitigation in fever, disappearance of cough, mitigation of lung signs, as well as the duration of hospital stay of all eligible patients were recorded.

Statistical analysis

All data were analyzed using SPSS 20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was employed for graph plotting. Counting data are presented as numbers and percentages {n (%)} and analyzed using the chi-square (χ^2) test. Measurement data are expressed as mean ± standard deviation (SD) and analyzed using a t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Treatment efficacy

The study group had a significantly higher clinical efficacy (88 %) than the control group (68 %) ($p < 0.05$) (Table 1).

TNF-α levels

Before treatment, the level of TNF-α in the control group and the study group were 8.76 ± 2.11 and 8.52 ± 2.14 ng/mL, respectively, and the differences between them were not statistically different ($p > 0.05$). After treatment, the levels of TNF-α in the control group and the study group were significantly decreased to 6.67 ± 0.90 (t = 6.442, $p < 0.001$) and 4.13 ± 1.24 ng/mL (t = 12.551, $p < 0.001$), respectively. Patients in the study group showed lower levels of TNF-α than those in the control group (t = 11.722, $p < 0.001$), as shown in Figure 1.

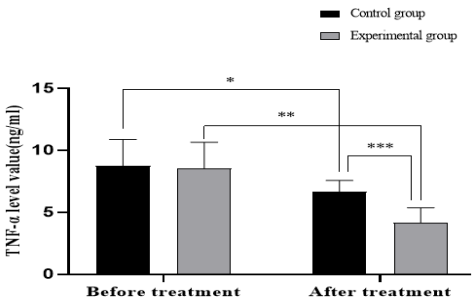

Figure 1: TNF-α levels before and after treatment in the two groups of children (mean ± SD)

IL-8 levels

Before treatment, the IL-8 levels of children in the control group and the study group were 17.65 ± 3.24 and 17.45 ± 3.16 pg/mL, respectively, which showed no significant inter-group differences ($p > 0.05$). After treatment, the levels of IL-8 of the control group and the study group were significantly decreased to 13.37 ± 4.03 (t = 5.853, $p < 0.001$) and 10.34 ± 4.12 pg/mL (t = 9.683, $p < 0.001$), respectively. Patients in the study group showed lower IL-8 levels than those in the control group (t = 3.718, $p < 0.001$), as shown in Figure 2.

CRP levels

Before treatment, the CRP levels in the control group and the study group were 15.74 ± 2.67 and 15.86 ± 2.73 mg/L, respectively, and there were no significant differences between them ($p > 0.05$). After treatment, the CRP levels in the control group and the study group were significantly reduced to 11.23 ± 2.15 and 9.72 ± 2.27 mg/L, respectively. The CRP levels of the study group were significantly lower than those of the control group (t = 3.415, $p < 0.001$) (Figure 3).

Table 1: Clinical efficacy of the two groups of children {n(%)}

Group	n	Cured	Markedly effective	Effective	Ineffective	Total effective
Control	50	23(46.00)	11(22.00)	10(20.00)	6(12.00)	34(68.00)
Study	50	29(58.00)	15(30.00)	5(10.00)	1(2.00)	44(88.00)
X^2						5.828
P-value						<0.05

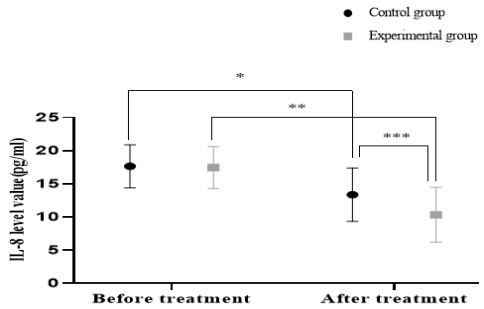

Figure 2: Comparison of IL-8 levels of the two groups of children before and after treatment (mean ± SD)

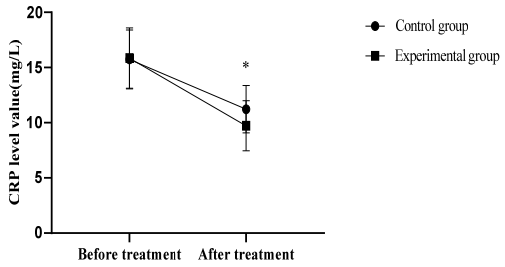

Figure 3: Comparison of CRP levels of the two groups of children before and after treatment (mean ± SD)

PCT levels

Before treatment, the PCT levels in the control group and the study group were 10.85 ± 3.14 and 10.67 ± 2.36 mg/L, respectively, and the differences between them were not significant (p > 0.05). After treatment, the PCT levels in the control group and the study group were significantly decreased to 8.36 ± 2.19 and 6.68 ± 1.47 pg/mL, respectively. The CRP levels of the study group were significantly lower than those of the control group (t = 4.504, p < 0.001) (Figure 4).

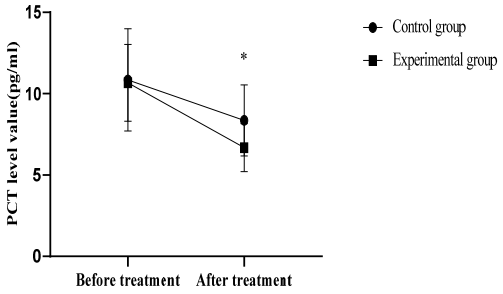

Figure 4: Comparison of the PCT levels of the two groups of children before and after treatment (mean ± SD)

Levels of immune function parameters

There were no significant differences in the levels of IgA, IgM, and IgG between the two groups of patients before treatment (p > 0.05). The patients in the study group showed significantly higher levels of IgA, IgM, and IgG than those in the control group (p < 0.05) (Table 2).

Time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay

Patients in the study group had a shorter time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay than those in the control group (p < 0.05), as indicated in Table 3.

Table 2: Comparison of the immune function of the two groups of children before and after treatment (mean ± SD, g/L, N = 50))

Group	IgA		IgM		IgG	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	1.61±0.33	2.43±0.48	1.76±0.46	2.26±0.44	5.37±1.24	6.48±1.14
Study	1.63±0.35	2.77±0.47	1.88±0.51	2.99±0.46	5.63±1.15	7.41±1.23
t	0.294	3.579	1.253	8.109	1.087	3.921
P-value	0.769	<0.001	0.22	<0.001	0.28	<0.001

Table 3: Time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay (mean ± SD, N = 50))

Group	Fever reduction	Disappearance of cough	Disappearance of pulmonary rales	Hospital stay
Control	5.02±0.45	5.03±1.13	5.88±1.24	11.46±2.56
Study	4.11±0.37	3.84±0.78	4.29±0.75	8.27±2.24
t	11.045	6.128	7.758	6.631
P-value	<0.001	<0.001	<0.001	<0.001

DISCUSSION

Mycoplasma pneumonia (MPP), a pathogenic microorganism with no cell wall, is considered intermediate between bacteria and viruses. It mainly infects the respiratory system and remains one of the major pathogens that cause respiratory tract infections in children [10]. Research has revealed that in addition to respiratory infections, MPP may also cause myocarditis, nephritis, and many other diseases in the immune system, leading to complicated infections [11]. Roxithromycin is a new generation of macrolide antibiotics that exerts an excellent bactericidal effect against anaerobic bacteria, gram-positive bacteria, mycoplasma, and chlamydia. Roxithromycin binds to the 50S ribosomal subunit of bacteria, resulting in the inactivation of mycoplasma, with a similar antibacterial effect but 1- 4 times stronger *in vivo* than erythromycin [12]. The distribution characteristics of roxithromycin in the body conform to the two-compartment model, with a time-dependent antibacterial effect, which suggests a promising therapeutic outcome [13,14]. Gamma globulin, the main effector molecule of the immune system, is produced by β cells of the lymphatic system [15]. Intravenous injection of gamma globulin leads to enhancement of the immune system and mitigation of toxic reactions, thereby ensuring complete elimination of viruses and bacteria [16-18]. A prior study has shown that roxithromycin plus gamma globulin had a satisfactory result in the treatment of MPP in children, with total effectiveness of 85.71 % [19]. In the present study, roxithromycin plus gamma globulin was associated with a higher efficacy (88 %) versus gamma globulin alone (68 %). In a previous study, inflammatory mediators were highly expressed in children with MPP, necessitating the monitoring of these inflammatory mediators during the treatment [20]. In the present study, the levels of TNF-α, IL-8, CRP, and PCT were decreased after treatment, with lower levels observed in patients using roxithromycin plus gamma globulin versus single therapy of gamma globulin. These results indicate that the combined use of roxithromycin and gamma globulin in the treatment of MPP in children effectively mitigates the inflammatory response. In addition, the patients receiving roxithromycin plus gamma globulin showed significantly higher levels of IgA, IgM, and IgG versus those given gamma globulin alone. This is in line with the results of Qin *et al* [21] who reported that the use of roxithromycin plus gamma globulin in the treatment of MPP in children enhanced the immunity of the patients. Furthermore, the shorter time lapse before fever reduction, cough disappearance, lung sign disappearance, and duration of hospital stay of patients given joint treatment versus single therapy indicates a promising treatment efficacy of roxithromycin and gamma globulin in children with MPP.

CONCLUSION

Roxithromycin combined with gamma globulin in the treatment of children with MPP has significant benefits in the treatment of children with MPP by mitigating inflammatory response, enhancing immunity, and alleviating clinical symptoms of MPP. Thus, the combination treatment shows good potentials for use in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. The authors contributed equally to this research.

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