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Effect of budesonide combined with vitamin C on the inflammation response of pediatric mycoplasma pneumoniae pneumonia

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Abstract: To observe the therapeutic effect of vitamin C combined with budesonide (BUD) on Mycoplasma pneumoniae (MP) pneumonia. A total of 106 children with MP admitted to our hospital from June 2021 to December 2024 were selected for the study. 57 children received vitamin C combined with conventional treatment (control group); the other 49 children were treated with vitamin C combined with BUD treatment (research group). The clinical efficacy of the two groups was compared and the time of disappearance of fever, cough and pulmonary wet rales was counted. Lung function, inflammatory factor and immunoglobulin levels were measured before and after treatment and adverse reactions were recorded. The results showed that the total effective rate of treatment in the study group was higher than that in the control group, while the time of fever, cough and disappearance of pulmonary wet rales was shorter than that in the control group ($P<0.05$). After treatment, the lung function of the study group was significantly better than that of the control group, while the level of inflammatory factors was lower than that of the control group ($P<0.05$). In addition, Immunoglobulins (Ig)A and IgM decreased and IgG increased in both groups after treatment, with the difference in the study group being more significant ($P<0.05$). Comparison of the incidence of adverse reactions between the two groups, on the other hand, showed no significant difference ($P>0.05$). These results suggest that the combination of vitamin C and budesonide may be of great value in the future treatment of MP pneumonia.

Keywords: Budesonide, mycoplasma pneumoniae pneumonia, vitamin C, immunoglobulin

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INTRODUCTION

Mycoplasma pneumoniae (MP) pneumonia has an incubation period of 2-3 weeks and is extremely common in adolescents and children (Meyer Sauteur *et al.*, 2020). The prevalence of MP pneumonia has been estimated to be as high as about 30-50% in people aged 5-15 years, accounting for about 40% or more of all pneumonia (Tsai *et al.*, 2021). The onset of MP pneumonia is often accompanied by clinical manifestations such as fever, dry cough under irritation and sore throat, which may cause serious complications such as chronic lung disease and exudative pleurisy if left untreated, endangering the health of children (Y. Xu *et al.*, 2024; Ha *et al.*, 2024). Among them, MP is also considered to be the main cause of repeated respiratory tract infections (RRTI) in children, which is a great burden on the normal development and physical and mental health of the children due to its long duration, severe symptoms, migration and recurrent episodes (Boonyaratanakornkit *et al.*, 2020).

At present, antibiotic drugs such as azithromycin (AZI) are usually used in clinical practice to treat MP pneumonia, but it is difficult to achieve the desired efficacy with single drug therapy (Peng *et al.*, 2022). Budesonide (BUD) is a non-halogenated steroid hormone that efficiently enhances the local anti-inflammatory effect and relaxes smooth muscle tension (Li *et al.*, 2022). Meanwhile, in the treatment of MP pneumonia, enhancing their immune function is also of great significance in controlling the progression of the disease (Zhu *et al.*, 2023). Vitamin C is one of the most important micronutrients in the human body, which can enhance the production of lymphocytes, improve the phagocytosis of phagocytes, promote the synthesis of immunoglobulins and improve the immunity of the body (Gordon *et al.*, 2020). In MP pneumonia, vitamin C supplementation may provide more reliable treatment for children.

Therefore, this study will observe the clinical effect of BUD combined with vitamin C in the treatment of MP pneumonia, observe the lung function of children before and after treatment, with the aim of providing reliable references and guiding opinions for future clinics in the diagnosis and treatment of MP pneumonia.

MATERIALS AND METHODS

Research subjects

We designed a retrospective analysis with a potential study population of children with MP admitted from June 2021 to December 2024 at our hospital. First, we calculated the number of study subjects using the G-Power software (a minimum of 42 cases per group was required when effect size=0.5, $\alpha=0.05$ and power=0.95) and with this criterion, we screened the potential study subjects based on inclusion exclusion and 106 study subjects were finally included. Among them, 57 children received vitamin C combined

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with conventional treatment and were considered as the control group; the other 49 children were treated with vitamin C combined with BUD treatment and were considered as the research group. All study participants were unaware of their subgroups. The study was approved by the Ethics Committee of our hospital and all immediate family members of the study subjects signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: The diagnosis of MP pneumonia was confirmed by qualitative and quantitative IgM antibody tests with fever and irritating cough, diffuse reticular shadow changes on chest X-ray, audible moist rales on lung auscultation and normal organ function. Exclusion criteria: those with combined familial genetic disease or malignancy, those with abnormal coagulation, those with severe pulmonary infections, airway foreign bodies or other chronic respiratory diseases and those with a history of other antibiotic-like drugs or immunosuppressive therapy within the last 3 months.

Treatment methods

Control group: After admission, all children were given intravenous AZI (Sinopharm Group Guorui Pharmaceutical Co., Ltd., H20030269) 10 mg/kg/d mixed with 5% glucose once/d for 5-7 d until children' body temperature returned to normal. At this time, children in the control group were switched to oral AZI Tablets (Pfizer Pharmaceuticals Ltd., H10960168) 10 mg/kg/d at a maximum dose of 0.5 g, 1 time/d. In addition, vitamin C injection (Shanghai Modern Hassan Pharmaceutical Co., Ltd, H41024222) 100 mg/kd/d was given with 100 mL of 10% dextrose solution intravenously once/d for 5 d and then discontinued for 4 d. The vitamin C injection was administered to the patients who had not received any vitamin C injection. Research group: On the basis of the control group, BUD (Zhengda Tianqing Pharmaceutical Group, H20203063) was given as nebulized inhalation in the control group, mixed with 2-3 mL of 0.9% sodium chloride injection (China Otsuka Pharmaceutical Co., Ltd, H20043271). Children aged 1-3 years inhaled 0.5 mg each time and those aged 4 years or older inhaled 1 mg each time, 2-3 times/d. One week was a course of treatment and both groups of children continued treatment for 2 courses.

Outcome measures

(1) Clinical efficacy (Meyer Sauteur *et al.*, 2021): cured: After treatment, the child's body temperature is normal, no clinical symptoms and moist rales in the lungs and 95-100 lung lesions are seen on X-ray; markedly effective: After treatment, the body temperature is normal and the lung lesions are 70-94% absorbed; effective: Lightly kissed clinical symptoms remain after treatment, with 20-69% absorption of lung lesions; ineffective: not meeting the above criteria or even aggravation of the disease. Total efficiency = cured rate + marked effective rate + effective rate. (2) Recovery: The time of fever, cough and disappearance of moist rales in the lungs of children were counted. (3) Pulmonary function: The forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) were measured before and after treatment using a pulmonary function instrument (Shanghai Hanfei Medical Equipment Co., Ltd, EasyOne Pulmonary Function Tester).

Higher FEV1, FVC and PEF indicate better pulmonary ventilation. (4) Inflammation: Venous blood was collected from children before and after treatment and hypersensitive-C reactive protein (hs-CRP) was measured using a fully automated hematology analyzer (BC-7500) and serum was obtained by centrifugation and the levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured by ELISA. The kits were purchased from Beijing Solarbio Science & Technology and the operation was carried out in strict accordance with the kit instructions. Higher hs-CRP, TNF-α and IL-6 indicate a stronger inflammatory response. (5) Immune function: immunoglobulins G/A/M (IgG/A/M) were measured before and after treatment using a protein analyzer (Siemens, BN-II). Higher IgG/A/M indicates better immune function. (6) Adverse reactions: adverse reactions during treatment in children, such as nausea and vomiting, headache, etc.

STATISTICAL ANALYSIS

SPSS 22.0 software was used for statistical analysis. The counting data [n (%)] were compared using chi-square tests, the measurement data were compared using ($\bar{\chi}\pm s$) using independent samples t-tests, paired t-tests. To control the Family-Wise Error Rate (FWER), the Bonferroni correction was used by adjusting the significance level to α/mα/m, where mm is the number of comparisons. For exploratory analyses with a large number of comparisons (e.g., >10), the Benjamini-Hochberg procedure was applied to control the False Discovery Rate (FDR). Adjusted P-values are reported where applicable. $P<0.05$ indicates that the difference is statistically significant.

RESULTS

Clinical efficacy

The clinical efficacy results of both groups of children revealed that the total effective rate of treatment in the research group was 91.84%, which was higher than that of 73.68% in the control group and the difference was statistically obvious ($P<0.05$) (table 1).

Rehabilitation

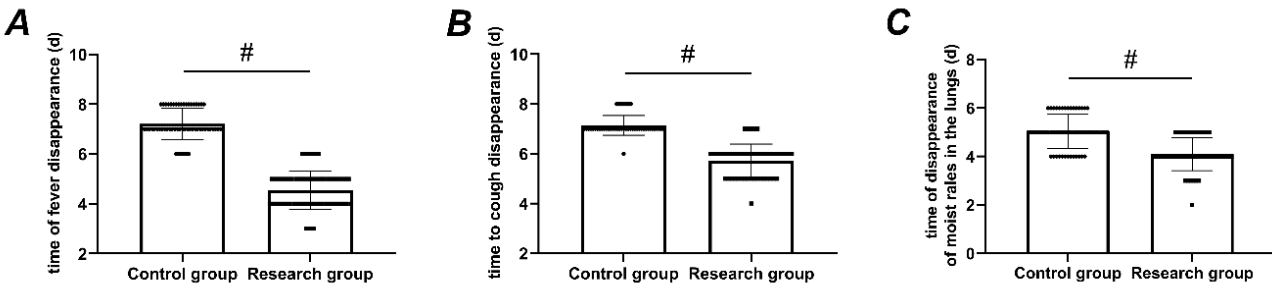
The time to disappearance of fever, cough and moist rales in the lungs of children in the research group were (4.55±0.77) d, (5.71±0.68) d and (4.10±0.68) d, respectively, which were shorter compared with the control group, with statistically obvious differences ($P<0.05$) (fig. 1).

Table 1: Clinical efficacy

	Cured	Markedly effective	Effective	Ineffective	Total efficiency rate
Control group (n=57)	16 (28.07)	19 (33.33)	7 (12.28)	15 (26.32)	73.68%
Research group (n=49)	22 (44.90)	18 (36.73)	5 (10.20)	4 (8.16)	91.84%
χ^2					5.902
P					0.151

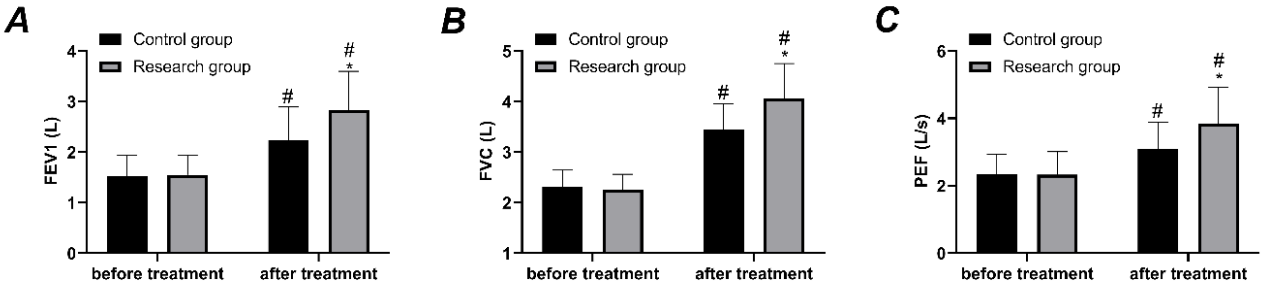
Table 2: Adverse reactions

	Gastrointestinal reactions	Rash	Bronchospasm	Vomiting	Poor appetite	Overall incidence rate
Control group (n=57)	2 (3.51)	1 (1.75)	1 (1.75)	2 (3.51)	0 (0.0)	10.53%
Research group (n=49)	2 (4.08)	1 (2.04)	2 (4.08)	1 (2.04)	1 (2.04)	14.29%
χ^2						0.346
P						0.556



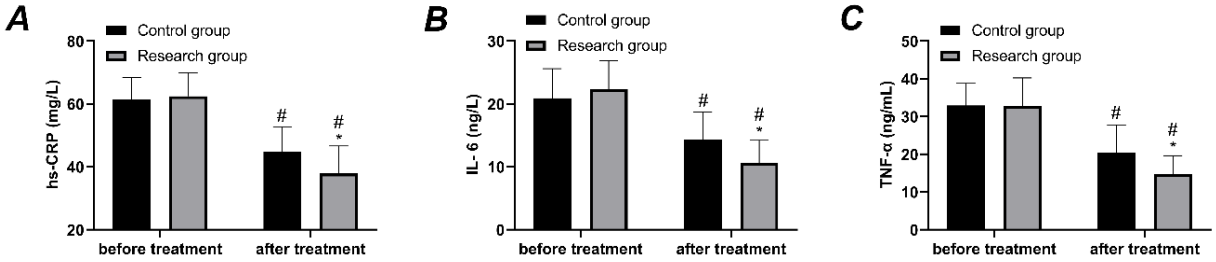
(A) Time of fever disappearance in children (95%CI: -2.926 to -2.939). (B) Time to cough disappearance of children (95%CI: -1.637 to -1.216). (C) Time of disappearance of moist rales in the lungs of children (95%CI: -1.202 to -0.664). #: the difference between the two groups was statistically significant (P<0.05).

Fig. 1: Rehabilitation.



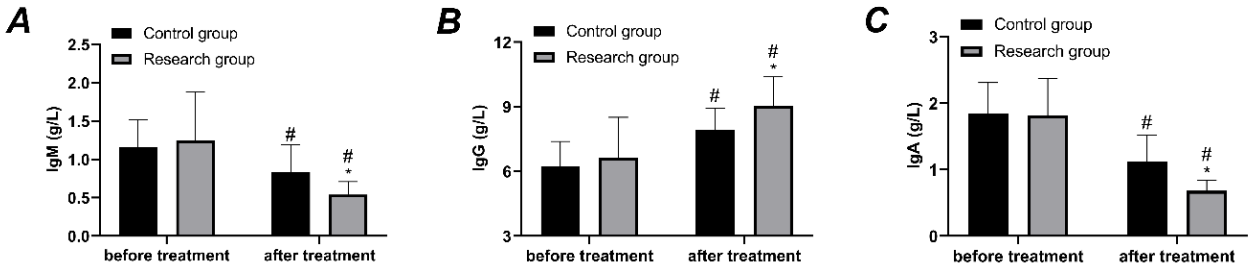
(A) FEV1 before and after the treatment. (B) FVC before and after the treatment. (C) PEF before and after the treatment. #: statistically significant difference from before treatment (P<0.05). *: statistically significant difference from control group (P<0.05). Forced expiratory volume in 1 second (FEV_1); Forced vital capacity (FVC); Peak expiratory flow (PEF).

Fig. 2: Lung function.



(A) Hs-CRP before and after the treatment. (B) IL-6 before and after the treatment. (C) TNF-α before and after the treatment. #: statistically significant difference from before treatment (P<0.05). *: statistically significant difference from control group (P<0.05). Hypersensitive-C reactive protein (hs-CRP); Tumor necrosis factor-α (TNF-α) Interleukin-6 (IL-6).

Fig. 3: Inflammation.



(A) IgM before and after the treatment. (B) IgG before and after the treatment. (C) IgA before and after the treatment. #: statistically significant difference from before treatment (P<0.05). *: statistically significant difference from control group (P<0.05). Immunoglobulins G/A/M (IgG/A/M).

Fig. 4: Immune function.

Lung function

Before treatment, there was no marked difference in pulmonary function between both groups of children (P>0.05). After treatment, FEV1, FVC and PEF increased to (2.84±0.76) L, (4.06±0.69) L and (3.85±1.07) L/s in the research group, while FEV1, FVC and PEF increased to (2.84±0.76) L, (4.06±0.69) L and (3.85±1.07) L/s in the control group, respectively. The comparison of pulmonary function between the two groups after treatment demonstrated that study groups were higher than the control group (P<0.05) (fig. 2).

Inflammation

Before treatment, there was no statistically remarkable difference in the inflammatory factor tests between both groups of children (P>0.05) and the results of hs-CRP, IL-6 and TNF-α tests were reduced in both groups after treatment (P<0.05). Among them, hs-CRP, IL-6 and TNF-α were lower in the research group than in the control group after treatment (P<0.05) (fig. 3).

Immune function

Immunoglobulin assay results denoted that IgA and IgM were lower in both groups after treatment and were lower in the research group than in the control group (P<0.05). While IgG was higher after treatment than before treatment; it was higher in the research group than in the control group and the difference was statistically obvious (P<0.05) (fig. 4).

Adverse reactions

Adverse reactions such as gastrointestinal reactions, rash and bronchospasm occurred during treatment in the research group of children, with an overall incidence of 14.29%. Adverse reactions such as vomiting and rash were also seen in the control group, with an overall incidence of 10.53%. The difference in the incidence of adverse reactions between both groups was not statistically remarkable (P>0.05) (table 2).

DISCUSSION

As an infectious disease, MP pneumonia is closely related to the immune function of children, therefore, how to improve the immune function of children largely determines the therapeutic effect of MP pneumonia (Pei *et al.*, 2021). In this study, we found that the treatment of children with MP pneumonia with vitamin C combined with BUD not only improved their clinical symptoms, but also significantly improved their inflammatory response

and immune function, which demonstrates the potential of vitamin C combined with BUD for future use in MP pneumonia.

It was seen that the clinical efficacy of children in the research group was better than that of the control group and the time to disappearance of fever, cough and moist rales in the lungs after treatment was also shorter ($P<0.05$), suggesting that vitamin C combined with BUD has a more efficient and excellent therapeutic effect on the treatment of MP pneumonia. Previous studies have pointed out that after nebulized inhalation of BUD, it can rapidly diffuse throughout the lungs, inhibit the release of inflammatory mediators from lung cells and provide local anti-inflammatory effects (F. Xu *et al.*, 2024; Chen *et al.*, 2023). The therapeutic efficacy of BUD for MP has been clinically recognized in previous studies (Li *et al*., 2022). And in a review report on COVID-19 positive female patients, Erciyestepe SG *et al*. also confirmed the excellent therapeutic efficacy of vitamin C in combination with BUD (Erciyestepe & Pata, 2024) and our results were similar. This was similarly confirmed when we compared the inflammation in the two groups of children and found lower levels of hs-CRP, IL-6 and TNF-α after treatment in the research group ($P<0.05$). Furthermore, BUD also has the ability to antagonize substances such as leukotrienes and platelet-activating factors, which can effectively reduce the stress load on airway smooth muscle cells and improve airway patency (Agusti *et al.*, 2022). Because of this, children in the research group also revealed a more significant improvement in lung function after treatment compared to the control group. Tsao PC *et al*. found that BUD alleviated oxidative stress in airway smooth muscle cells of rats with pneumonia (Tsao *et al.*, 2021), which can also corroborate the results of the current experiment, suggesting that the application of BUD has a more desirable effect on improving the respiratory status. Moreover, a more significant decrease in IgA and IgM and an increase in IgG were seen in the research group ($P<0.05$), which suggests that vitamin C combined with BUD may also be more effective in improving the immune function of MP children. The reason for this may be related to the fact that BUD reduces the release of allergy-active mediators such as histamine by enhancing the stability of smooth muscle cells and lysosomal membranes (Daval *et al.*, 2020). It is well known that MP pneumonia, as an infectious respiratory disease, the immune function of the affected child's organism plays a decisive role in the defense against pathogenic bacterial infections (de Groot *et al.*, 2022). The improvement of immune function in the research group not only contributes to the recovery of children, but also enables their prognosis to avoid re-infection of MP and provides a more reliable guarantee for their healthy growth. Periasamy N *et al*. mentioned that the use of BUD did not alter the immune function of patients with allergic rhinitis (Periasamy *et al.*, 2020), which is inconsistent with the results of the current study and it is speculated that the difference may be due to different pathogenic mechanisms. To verify this, we should subsequently add the detection of indicators such as T-lymphocyte subsets during vitamin C combined with BUD therapy. In addition, some studies have suggested that overdosing on vitamin C may cause diseases such as kidney stones (Gruber-Bzura, 2022). In this study, we can see that there is no significant difference in the incidence of adverse reactions between the two groups of children, which indicates that the dose of vitamin C used in this sub-study is appropriate and the combination of the two will not increase the toxicity of side effects, which is of high clinical value.

As this study was a single-center retrospective analysis, the smaller number of cases may have led to biased results. Also, we could not further emphasize the effect of vitamins combined with BUD on children with MP because we could not set up a placebo control group. Also, due to the short follow-up period, we were unable to assess the long-term prognosis of the children. In the follow-up study, we will also conduct a more in-depth and comprehensive experimental analysis on the application of vitamin C in combination with BUD in MP pneumonia, so as to provide more reliable clinical references.

CONCLUSION

Compared to AZI combined with vitamin C, BUD combined with MP improves lung function and immune function in children better, while suppressing the increase in inflammatory response. At the same time, the regimen does not increase adverse effects in children.

Conflict of interest

There is no conflict of interest.

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