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Original Research Article

Gamma globulin improves pulmonary function and increases C3 and C4 serum levels of septic children in pediatric intensive care unit

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Abstract

Purpose: *To probe into the effects of gamma globulin on the pulmonary functions, and C3 and C4 serum levels of septic children in pediatric intensive care unit (PICU).*
Methods: *Sixty-seven children with sepsis were retrospectively analyzed and assigned into study group (SG, n = 36) and control group (CG, n = 31) based on treatment modalities. The children in CG received conventional sepsis treatment, while children in SG were treated with gamma globulin. Differences in pulmonary function as well as C3 and C4 serum levels were compared in both groups before and after treatment. Children in SG were assigned into mild group (n = 21) and severe group (n = 15) in based on the severity of their conditions.*
Results: *After treatment, SG showed higher forced vital capacity (FVC) and peak expiratory flow (PEF) than CG ($p < 0.05$). SG also showed higher C3 and C4 serum levels than CG after treatment ($p < 0.05$).*
Conclusion: *Administration of gamma globulin to children in PICU significantly improves lung function and increases their serum C3 and C4 levels. C3 and C4 serum levels of septic children in PICU correlate with prognosis. Hence, C3 and C4 can be regarded as indicators for the diagnosis, evaluation and prognosis of septic children in PICU.*

Keywords: *Gamma globulin, Pediatric intensive care unit, Sepsis, Pulmonary function, Serum complement, Impact analysis*

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INTRODUCTION

Pneumonia is one of the common disorders in pediatrics [1]. Due to the physiological and anatomical characteristics of the respiratory system and the imperfect autoimmune and defense functions in children, the incidence of pneumonia is high [2]. In infants especially, the clinical symptoms and signs of pneumonia are subtle and easily ignored, leading to delay in diagnosis and treatment, and the development of severe pneumonia [3]. Epidemiological data shows that from 2000 to 2015, there were more than 100 million cases of pneumonia in children under the age of five in developing countries, and more than 900,000 died from pneumonia [4]. Severe pneumonia accounted for more than 16 % of pneumonia cases, and is still showing a

yearly increase [5]. Sepsis is one of the serious complications of severe pneumonia in children, with a mortality rate of more than 25 %. Sepsis has been confirmed as an independent risk factor for death from severe pneumonia in children, and children with sepsis tend to have a poor prognosis [6].

Serum complement is a key component of an individual's response to pathogenic infection, which is widely present in human serum and tissue fluid, and mediates immune and inflammatory responses [7]. Serum C3 and C4 complements in serum are much higher than those of other complement molecules [8]. Both of them exert crucial roles in multiple functions of the complement system, and are often used clinically in the diagnosis, treatment, and etiological investigation of diseases [9]. Gamma globulin, also known as immunoglobulin, is often used clinically to treat immunodeficiency diseases, as well as infectious hepatitis and herpes zoster because of its ability to enhance immunity and prevent infection [10]. There have been clinical reports on the administration of gamma globulin in treating sepsis, and the findings have confirmed that it significantly improved the immune function of patients with sepsis, and has positive significance in accelerating their regression [11]. However, there is still a gap in research on how gamma globulin affects serum complement in septic children. The purpose of this research was to probe into the feasibility of using gamma globulin in the treatment of children with sepsis in PICU by setting up a control group and analyzing its effect on complement C3 and C4 serum levels, so as to provide clinical reference for improving the prognosis of children in PICU.

METHODS

General data

Clinical data of 67 children with sepsis treated in West China Second University Hospital, Sichuan University from June 2019 to December 2021 were retrospectively collected and assigned to the control group (n = 31) and the study group (n = 36) in accordance with the different treatment modalities. The research was approved by the Ethics Committee of West China Second University Hospital, Sichuan University (approval no. 2020(111)), and the research involving human subjects conformed to ethical norms and standards in the Declaration of Helsinki [12]. The parents of the study subjects signed informed consent to allow the use of clinical data.

These included children were those who met the diagnostic criteria of the Chinese Expert Consensus on the Diagnosis and Treatment of Childhood Sepsis (2015 version) [13], those who were aged between 28 days and 14 years, children with complete and available clinical data, and children with concurrent pneumonia.

The excluded children were those with incomplete clinical data, those with severe coagulation dysfunction and hematologic disorders, those with severe metabolic acidosis, those with serious diseases of the liver, kidney, brain, and other organs, those with congenital heart disease, those with significant edema of the lung tissue, those with allergy to gamma globulin, and those with uremic encephalopathy, uremic pericarditis, or hyperthermia.

Interventions

Children in the control group received conventional crystalloid fluid for resuscitation, to correct water-electrolyte disorders as well as nutritional support, active control of infection and treatment of primary diseases. Dopamine injection was administered to maintain blood pressure in cases of blood pressure derangement. Antibiotics and mechanical ventilation were provided where necessary.

The children In the study group were treated with gamma globulin (Shanxi Kangbao Biological Products Co. Ltd., S19994004) at a dose of 400 mg/kg once a day, via intravenous infusion for 3 days. Both groups were observed for 14 days.

Observations

Primary indicators

(1) The changes in forced vital capacity (FVC) and peak expiratory flow (PEF) were measured using a pediatric pulmonary function tester to evaluate the role of treatment in the pulmonary function of the children.

(2) The measurement of C3 and C4 serum levels were performed before and after treatment in both groups. Fasting elbow venous blood was harvested before and then 14 days after treatment. After the samples were collected and centrifuged at 3000 rpm, the measurement of C3 and C4 serum levels was implemented using enzyme-linked immunosorbent assay (ELISA), which was conducted strictly according to the kit instructions. The average value of each index was obtained three times as the final result.

Secondary indicators

(1) According to the diagnostic criteria of the "Expert Consensus on the Diagnosis and Treatment of Childhood Sepsis in China (2015 version)" [13], the enrolled children were allocated into severe group (n = 15) and mild group (n = 21) in accordance with severity of disease, and C3 and C4 were compared between severe and mild cases as well.

(2) The enrolled children were assigned to survival group (n = 30) and death group (n = 6) based on different outcomes of follow-up, and the C3 and C4 serum levels were compared between the survival and death cases.

(3) The diagnostic ROC curves of C3 and C4 on the clinical outcomes of children were plotted. The area under the curves (AUCs) of C3, C4, and C3 + C4 on clinical outcomes of children with sepsis were computed, respectively.

Statistical analysis

Data analysis were implemented using Statistical Package for the Social Sciences (SPSS) 24.0 statistical software (IBM, Armonk, USA). Kolmogorov-Smimov test was applied for normality of quantitative data. Indices with normal distribution were analyzed using the independent samples t-test, and post hoc comparisons were made using the SNK test, with results described by mean ± standard deviation (SD). Indices without normal distribution were analyzed using the Kruskal Wallis rank sum test, with data described by median and quartiles. Group comparisons of qualitative data were implemented using chi-square test. $P < 0.05$ denoted statistically significant differences. Figures were plotted with GraphPad Prism 8.3 [14].

RESULTS

Comparison of clinical data

Clinical data in terms of age, sex, body mass, underlying disease, white blood cells (WBC) and platelets (PLT) count showed no significant differences in both groups ($p > 0.05$) (Table 1).

Changes in pulmonary function Indices

Both groups showed no significant differences in FVC and PEF values before treatment ($p > 0.05$). After treatment, the study group exhibited significantly higher FVC and PEF values than the control group ($p < 0.05$), and both groups of the children exhibited higher FVC and PEF values than before treatment ($p < 0.05$) (Table 2 and Figure 1).

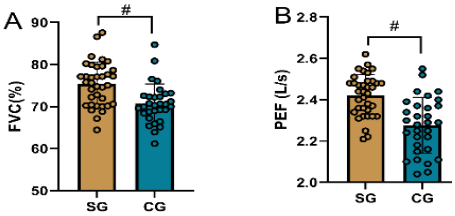

Figure 1: Changes in pulmonary function Indices after treatment. After treatment, the study group exhibited higher levels of FVC (A) and PEF (B) than the control group. $^{\#}p < 0.05$ versus the control group

Table 1: Comparison of baseline data (mean ± SD)/(n (%))

Baseline data		Study group (n=36)	Control group (n=31)	t/χ^2	*p*-value
Sex	Male	20	17	0.008	0.928
	Female	16	14		
Mean age (years)		5.66±2.03	6.12±1.73	0.989	0.326
Mean BMI (kg/m^2)		15.96±2.09	15.34±2.30	1.156	0.252
Mean body mass (kg)		20.42±4.88	20.39±3.18	0.029	0.977
Underlying disease	Premature birth	4	4	1.025	0.635
	Malnutrition	2	3		
	Developmental backwardness	4	2		
WBC count (×10^9/L)		15.72±1.49	15.61±1.71	0.281	0.780
PLT count (×10^9/L)		196.74±12.25	196.92±12.02	0.060	0.952

Table 2: Changes in pulmonary function (mean ± SD)

Group	Number of cases	FVC (%)		PEF (L/s)	
		Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Study	36	56.85±8.78	75.40±5.22	2.15±0.54	2.42±0.10
Control	31	56.42±6.21	70.67±4.70	2.06±0.19	2.28±0.13
T	-	0.228	3.871	0.881	4.976
P-value	-	0.82	<0.001	0.382	<0.001

Changes in C3 and C4 serum levels

Both groups showed no significant differences in C3 and C4 serum levels before treatment ($p > 0.05$). After treatment, the study group exhibited significantly higher C3 and C4 serum levels than the control group ($p < 0.05$). Both groups showed higher C3 and C4 levels after treatment than before treatment ($p < 0.05$) (Figure 2).

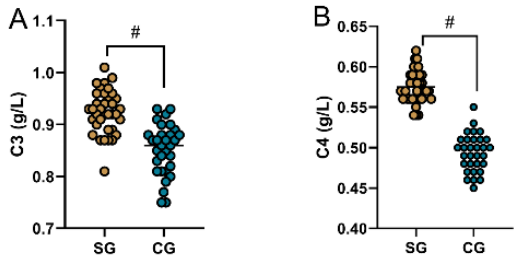

Figure 2: Serum C3 and C4 levels after treatment. After treatment, the study group exhibited significantly higher C3 (A) and C4 (B) serum levels than the control group. # $p < 0.05$ versus control group

Differences in C3 and C4 serum levels

The severe group showed lower C3 and C4 levels than the mild group ($p < 0.05$) (Figure 3). The survival group showed higher C3 and C4 levels than the death group ($p < 0.05$) (Figure 4).

Predictive values of C3 and C4 for prognosis of sepsis

The evaluation showed that with a cut-off value of 0.786 g/L, the AUCs of serum C3, C4, and the C3 + C4 (combined) for prognosis of septic children in PICU were 0.8861 ($p = 0.0032$), 0.8500 ($p = 0.0075$), and 0.9222 ($p = 0.0013$), respectively (Table 3, Figure 5).

DISCUSSION

Pediatric pneumonia is a leading cause of hospitalization and death in children, and this can lead to serious economic burden on the family of the children and affect the subsequent quality of life [15]. Pneumonia in children is more likely to develop into severe pneumonia due to the imperfect immune function of children, weak voluntary cough, poor ciliary motility, and low levels of immunoglobulins [16]. A study involving 147 children suffering from severe pneumonia indicated that the younger the age, the worse the prognosis of the children, with infants accounting for 71.8 % of those with a poor prognosis [17].

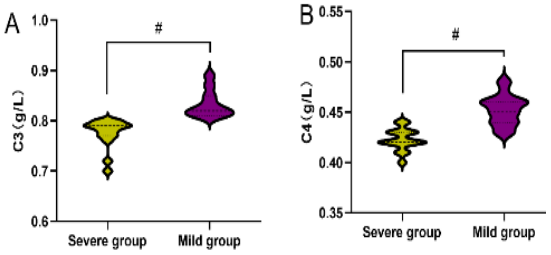

Figure 3: Comparison of C3 and C4 serum levels among children with various conditions. The severe group exhibited lower C3 (A) and C4 (B) than the mild group. #$p < 0.05$ versus mild group

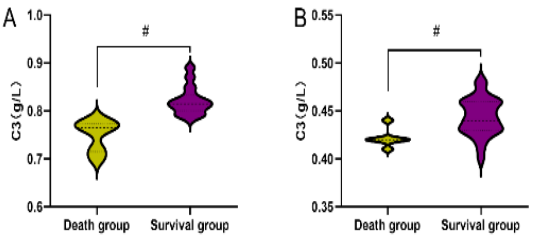

Figure 4: Comparison of serum C3 and C4 levels among children with different outcomes. The death group showed lower C3 (A) and C4 (B) than the survival group. #$p < 0.05$ versus survival group

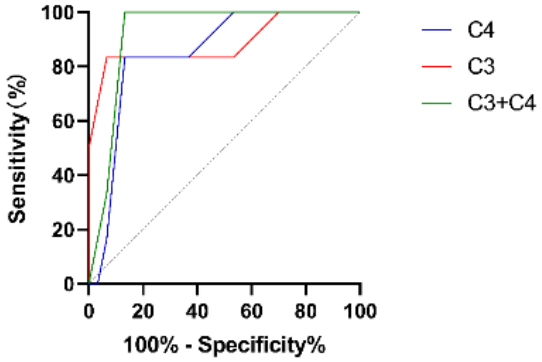

Figure 5: The value of C3 and C4 in prognostic assessment of septic children in PICU

Table 3: Analysis of the predictive values of C3 and C4 for prognosis of children with sepsis in PICU

Index	Cut-off value (g/L)	Sensitivity (%)	Specificity (%)	AUC	95% CI	SE	*p*-value
C3	0.76	83.33	93.33	0.8861	0.6993-1.000	0.095	0.003
C4	0.43	83.33	86.67	0.8500	0.7033-0.9667	0.075	0.008
C3+C4	0.76 or 0.43	98.18	86.67	0.9222	0.8340-1.000	0.045	0.001

Sepsis is a common complication of severe pneumonia, which is a syndrome of systemic inflammatory response characterized by infection, inflammation, and extensive chronic injury [18]. With complex clinical manifestations, patients are prone to one or more organ dysfunction or failure, and it is the main cause of death in clinical patients, with the mortality rate as high as 31 % [19]. The current treatment options for sepsis are still based on symptomatic supportive therapy such as anti-infection and fluid support, as there is still a lack of specific therapeutic intervention. It has been found that in the early stage of sepsis, pathogenic bacteria invades the body and causes an excessive inflammatory response, and as the disease worsens, the inflammatory response gradually becomes unbalanced and impairs immune function [20]. This suggested that improving the individual immune response may be one of the ways to improve the prognosis of septic patients.
The current research analyzed the clinical value of gamma globulin in improving pulmonary function and serum immune complement levels in children with sepsis. The findings revealed that in contrast with the control group of children on supportive therapy alone, the study group treated with gamma globulin had significantly higher levels post-treatment pulmonary function indicators (FCV and PEF), suggesting that gamma globulin effectively improved the pulmonary function of children with sepsis. A research of 120 septic children revealed that the combination of cefotaxime and gamma globulin significantly reduced the serum C-reactive protein and calcitoninogen levels, and improved the pulmonary function Indices, shortening the time to remission of clinical symptoms and their hospitalization time [21]. Another study showed that gamma globulin shortened the temperature recovery time and reduced the morbidity and mortality rate in septic children, as well as significantly having to reduce the serum C-reactive protein and calcitoninogen levels in children after treatment [22]. The current study concluded that gamma globulin is an immunomodulator with antiviral, antibacterial, and immune modulating functions, and its specific component is IgG, which significantly enhanced the efficacy of antibiotics by co-administration. Gamma globulin improves the immune status of the children with sepsis and regulates lung function [23]. This is also reflected in the present study that the study group exhibited higher C3 and C4 serum levels than the control group after intervention.

The current study further probed into the feasibility of the prognostic assessment of septic children using serum C3 and C4. The results showed that the C3 and C4 serum levels were significantly lower in children with severe condition than those in the mild group, and were higher in survival group than in death group, suggesting that serum C3 and C4 levels may be correlated with the prognosis of septic children. The value of C3 and C4 in the prognosis assessment of septic children was calculated by plotting ROC curves. The findings revealed that the AUCs of serum C3, C4, and C3 + C4 for the prognosis of septic children in PICU were 0.8861, 0.8500, and 0.9222, respectively.

A clinical study of 217 patients with sepsis revealed [24] that reduced C3 and C4 were independent risk factors for renal injury, and low C3 and C4 levels could be used to predict sepsis-related renal injury. It was reported that complement system has been considered to exert a crucial part in the development and progression of sepsis. The activation of complement can defend the body against pathogenic bacteria in the early stages of sepsis, while in the later stages of sepsis, lower complement levels often indicate organ damage and abnormalities in the coagulation and fibrinolytic system [25]. Therefore, the detection of serum complement C3 and C4 levels can provide a better understanding of sepsis in children. The prognosis of septic children can be evaluated to some extent by measuring C3 and C4 levels.

The novelty of this study is that differences in C3 and C4 levels among patients with different conditions and prognoses were calculated by means of quantitative analysis. This provided a new index for assessing the prognosis in septic children. The shortcomings of this study are the short duration of follow-up on the one hand, and the inclusion of a single sample source on the other hand, which will be improved at a later stage.

CONCLUSION

The administration of gamma globulin to children in PICU significantly improve lung function and increase C3 and C4 levels. The C3 and C4 serum levels of septic children in PICU correlate with their prognosis, so serum C3 and C4 can be considered for the diagnosis, assessment and prognosis of pneumonia induced sepsis in children.

DECLARATIONS

Acknowledgements

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Funding

None provided.

Ethical approval

This study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University, China (approval no. 2020(111)),

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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.

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