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Curative effects of vancomycin and cefotaxime combined with gamma globulin respectively in neonatal septicemia and their influences on PCT, CRP and hs-CRP

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Abstract. – OBJECTIVE: To explore the curative effects of vancomycin and cefotaxime combined with gamma globulin respectively in neonatal septicemia and their influences on PCT, CRP, and hs-CRP, so as to provide references for clinical treatment.

PATIENTS AND METHODS: 181 patients with neonatal septicemia admitted to Huangshi Maternity and Child Health Hospital from April 2012 to August 2014 were selected as the study subjects. Patients treated with vancomycin combined with gamma globulin were selected as group A (96 cases) and those treated with cefotaxime combined with gamma globulin were selected as group B (85 cases). The improvement time of clinical symptoms (milk rejection, nervous system symptoms, body temperature), hospital stays, mortality, medicine curative effects, adverse reactions, complications, and levels of serum CRP, PCT, and hs-CRP of patients before and after treatment were compared between the two groups.

RESULTS: The improvement time of clinical symptoms like body temperature, milk rejection, and neurological symptoms, as well as hospital stays in group A were lower than those in group B ($p<0.05$); the total effective rate of medicine curative effects in group B was better than that in group A ($p<0.05$); there was no significant difference in levels of serum CRP, PCT, and hs-CRP between the two groups before treatment ($p>0.05$); after treatment, levels of serum CRP, PCT, and hs-CRP in both groups decreased significantly, and levels of serum CRP, PCT, and hs-CRP in group B decreased more significantly than those in group A ($p<0.05$).

CONCLUSIONS: Cefotaxime combined with gamma globulin in the treatment of patients with neonatal septicemia has short improvement time in clinical symptoms, high total effective rate of drugs, low mortality, fewer adverse reactions and complications, and can significantly reduce levels of serum CRP, PCT, and hs-CRP, which is worthy of further promotion and application in clinical practice.

Key Words:
Neonatal septicemia, Vancomycin, Cefotaxime, Gamma globulin, PCT, CRP, hs-CRP.

Introduction

Neonatal septicemia is a serious infectious disease, which is prone to occur in newborns and characterized by signs of systemic infection accompanied by bacteremia in the first month after birth[1]. Most of them are caused by gram-positive cocci infection, which has the characteristics of insidious onset, rapid disease progression, and critical illness, seriously threatening the life safety of newborns[2]. Clinically, in the early stage of septicemia, neonatal patients are usually treated with combined antimicrobial agents, and appropriate antimicrobial agents are selected according to the results of drug sensitivity test after blood culture[3]. This leads to the long-term abuse of antimicrobial drugs, the increase of drug-resistant strains, and unsatisfactory conventional antibiotic treatments[4]. Therefore, how to effectively and rationally use antibacterial drugs has become a social problem worthy of discussion[5].

Vancomycin is an aminoglycoside antibiotic, which has outstanding effects in resisting drug-resistant bacteria with small adverse reactions[6]. Cefotaxime, the first-choice antibiotic for neonates in

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the third generation of cephalosporins, has broad antibacterial spectrum. It can kill pathogenic bacteria resistant to penicillin and aminoglycosides and is effectively against both Gram-positive bacterium and Gram-negative bacterium. It is also the preferred antibiotic for the treatment of neonatal septicemia[7,8]. As an immune enhancer, gamma globulin not only has double functions of immune substitution and immune regulation, but also has the effect of antiviral. At present, several clinical studies have confirmed that gamma globulin has certain therapeutic effects on neonatal septicemia[9].

PCT level of children with neonatal septicemia will significantly increase during the acute period, and other factors will not affect it[10]. CRP plays a very important role in tissue injury repair and is one of the most sensitive and rapid biomarkers for the assessment of acute reactions[11]. Hs-CRP is an acute phase reaction protein (APRP) synthesized by liver cells when the human body is invaded by microorganisms or suffers tissue damage[12]. All three are acute phase reaction proteins.

Currently, there are many studies[13,14] on the treatment of neonatal septicemia by vancomycin and cefotaxime. However, there are few researches on the specific therapeutic effects of vancomycin and cefotaxime combined with gamma globulin respectively and their influences on levels of serum PCT, CRP, and hs-CRP. We aim to observe the clinical efficacy of vancomycin and cefotaxime respectively combined with gamma globulin in the treatment of neonatal septicemia and their influence on levels of serum PCT, CRP, and hs-CRP, so as to provide references for clinical treatment.

Patients and Methods

Patients

A total of 181 patients with neonatal septicemia admitted to Huangshi Maternity and Child Health Hospital from April 2012 to August 2014 were selected. Patients treated with vancomycin combined with gamma globulin were selected as group A (96 cases) and those treated with cefotaxime combined with gamma globulin were selected as group B (85 cases). Among them, 50 males and 46 females in group A were aged from 1 to 29 days, the average age was (7.36±2.95) days, the birth weight was 2059-4635 g, and the average weight was (1819.65±406.35) g. In group B, 48 males and 37 females were aged from 2 to 26 days, the average age was (7.06±2.83) days, the birth weight was 2024 to 4536 g, and the average weight was (1864.06±375.28) g.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: this study was approved by the Ethics Committee of Huangshi Maternal and Child Health Hospital; of Edong Healthcare; all the families of the children were informed and signed a full informed consent form; the diagnostic criteria of neonatal septicemia were met; none was treated before hospitalization. The exclusion criteria were as follows: children with congenital immune dysfunction with severe birth defects, children with other organic diseases such as heart, liver and kidney, children allergic to cefotaxime, vancomycin, and gamma globulin, and children with severe birth defects.

Methods of Treatment

Both groups received symptomatic treatment and supportive treatment after hospitalization, i.e., comprehensive monitoring of blood gas and blood oxygen of children was put into effect, adequate nutritional support was provided, shock and acidosis were corrected, and hypoxemia and brain edema were effectively prevented. On this basis, children in group A were injected with vancomycin hydrochloride (CJ CheilJedang Corporation Company, Approval No.: H20100289); medicine methods: 15 mg/kg for age <7 days, once every 12 h; the daily dose was 15 mg/kg for age between 7 and 28 days, once every 8 h; the duration of each dose should be at least 60 min, and the intravenous micro-dosage pump should be employed. Group B was given a dose of 100 mg/(kg·d) cefotaxime (Shiyao Zhongnuo Pharmaceutical co., LTD., SFDA Approval No: H43200022) with intravenous injection, divided into two injections; on this basis, the dose of intravenous injection with 400 mg/(kg·d) of gamma globulin was increased in the two groups (Tonglu Biological Pharmaceuticals co., LTD., SFDA Approval No: s20063139), the drip rate was kept at 4 to 6 drops/min at the beginning, and if no adverse reaction was observed within 30 min, the drip rate could be appropriately accelerated, and the infusion was completed within about 2 h, once a day. Both groups were treated for 14 days for 1 course.

Evaluation of Efficacy

All subjects were evaluated for clinical efficacy after a month of treatment. Significantly effective: after treatment, the clinical symptoms were significantly improved, the skin of patients returned to ruddy, the body temperature was normal and stable, patients were able to eat normally, the results of bacterial culture were negative and the inspection

results of cerebrospinal fluid were normal; effective: the clinical symptoms improved after treatment, and the inspection results of bacterial culture or cerebrospinal fluid improved; ineffective: the clinical symptoms were not improved or even worsened after treatment, and the bacterial culture results were still positive. Significantly effective rate + effective rate = total effective rate. Adverse reactions of group A and group B during treatment were observed. The main adverse reactions were nausea and vomiting, rash, diarrhea, phlebitis, increased aminotransferase, etc.

Main Instruments and Reagents

PCT enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Yihe Biotechnology co., LTD., China, YH0811); CRP diagnostic kits (Wuhan Chundu Biology co., LTD., China, CDJ-1296C-SJH); hs-CRP diagnostic kits (Hepeng Biological Trade co., LTD., China, HPBIO-JC298); humaStar 600 automatic biochemical analyzer (Human, Germany, 16660); enzyme-linked immunosorbent assay (ELISA) detector (Molecular-Devices, SpectraMaxiD5, San José, CA, USA).

Methods of Detection

Levels of serum CRP and hs-CRP of the two groups before and after treatment were detected by immune scattered nephelometry. According to the manual of CRP and hs-CRP kits, the detection was carried out using the fully automated biochemical analyzer. PCT expression levels in serum of the two groups before and after treatment were detected by enzyme-linked immunosorbent assay (ELISA): the corresponding micropores of samples were numbered sequentially. Each plate should have 2 holes of negative control, 2 holes of positive control, and 1 hole of blank control. 100 μl of negative control and positive control were added into negative and positive control holes respectively. Then, 50 μl sample diluent was added into the sample hole to be tested, and then 50 μl samples to be tested, shaken gently, and mixed well. Closure plate membrane was used for closure plate, and then the plate was incubated at 37°C for 30 min. Distilled water was added into 30 times of concentrated washing solution to 1000 ml for backup. The closure plate membrane was carefully removed, the liquid was discarded. After dried, each hole was filled with washing solution, which was discarded after 30 s of standing, and this procedure was repeated for 5 times. 50 μl of enzyme-labeled reagent was added to each hole except for the blank hole. After incubation and washing again, 50 μl of the developer A and then 50 μl of the developer B were successively added to each hole, gently shaken and mixed, developing at 37°C in the dark for 15 min; 50 μl of stopping solution was added to each hole to terminate the reaction; the absorbance of each hole was measured sequentially at a wavelength of 450 nm by a BIV-TEK INSTRUMENTS INC with zero setting of a blank air conditioner. Measurement should be made within 15 min after the addition of the stopping solution.

Statistical Analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis, the counting data were represented by [n(%)], the measurement data were expressed as mean ± standard deviation (x±sd), the Chi-square test was used to compare the counting data between groups, the independent sample *t*-test was used to compare the measurement data between groups, paired *t*-test was verified for before and after comparison in groups. When $p<0.05$, the difference was statistically significant.

Results

General Materials

Comparison of clinical data between the two groups showed that there was no statistic difference in gender, days of birth, birth weight, gestational age, head circumference, smoking history of parents, alcoholism history of parents, place of residence of parents, body temperature, red blood cells, white blood cells, and delivery mode between the two groups ($p>0.05$; Table I).

Clinical Efficacy of the Two Groups

In group A, 50 cases (52.08%) showed significant effects after treatment, 19 cases (19.79%) were effective, 27 cases (28.13%) were ineffective, 13 cases (5.32%) were sick and died, and 57 cases (59.38%) of blood culture were turned negative. The total effective rate was 71.87%; in group B, 51 cases (60.00%) showed significant effects after treatment, 24 cases (28.24%) were effective, 10 cases (11.76%) were ineffective, 4 cases (4.71%) were sick and died, and 63 cases (74.12%) of blood culture turned negative, with a total effective rate of 88.24%. The total effective rate of group B after treatment was significantly higher than that of group A ($p<0.05$), and the fatality rate was significantly lower than that of group A ($p<0.05$; Table II).

Table I. Clinical data of patients [n (%)] (x±SD).

Factor		Group A (n=96)	Group B (n=85)	t/χ^2-value	*p*-value
Gender				0.350	0.554
	Male	50 (52.08)	48 (56.47)		
	Female	46 (47.92)	37 (43.53)		
Days of birth (d)		7.36±2.95	7.06±2.83	0.696	0.487
Birth weight (g)		1819.65±406.35	1864.06±375.28	0.761	0.448
Gestational age (week)		33.86±1.26	33.54±1.42	1.606	0.110
Head circumference (cm)		30.98±2.25	31.47±1.96	1.553	0.122
Height (cm)		42.12±4.25	41.68±4.12	0.705	0.482
Smoking history of parents				0.664	0.415
	Yes	51 (53.12)	40 (47.06)		
	No	45 (46.88)	45 (52.94)		
Alcoholism history of parents				0.008	0.928
	Yes	22 (22.92)	19 (22.35)		
	No	74 (77.08)	66 (77.65)		
Place of residence of parents				0.099	0.753
	City	68 (70.83)	62 (72.94)		
	Country	28 (29.17)	23 (27.06)		
Body temperature (°C)		36.70±0.31	36.72±0.29	0.447	0.656
Red blood cells ($\times10^{12}$/L)		6.59±0.52	6.62±0.48	0.402	0.689
White blood cells ($\times10^{9}$/L)		12.25±3.56	12.31±3.62	0.112	0.911
Delivery mode				0.956	0.328
	Eutocia	60 (62.50)	59 (69.41)		
	Cesarean	36 (37.50)	26 (30.59)		

Adverse Reactions in the Two Groups

In group A, there were 4 cases of nausea and vomiting (4.17%), 3 cases of rash (3.13%), 5 cases of diarrhea (5.21%), 2 cases of phlebitis (2.08%), 3 cases of elevated aminotransferase (3.13%), and the total prevalence of adverse reactions was 17.71%. In group B, there were 3 cases of nausea and vomiting (3.53%), 4 cases of rash (4.71%), 3 cases of diarrhea (3.53%), 2 cases of phlebitis (2.35%), and 3 cases of elevated aminotransferase (3.53%), with a total adverse reaction rate of 17.65%. There was no significant difference between group A and group B in the occurrence of nausea, vomiting, rash, diarrhea, phlebitis, and elevated aminotransferase ($p>0.05$; Table III).

Comparison of Improvement of Relevant Clinical Symptoms Between the Two Groups

The improvement time and hospitalization stay of clinical symptoms such as body temperature, milk rejection, and neurological symptoms in group A were higher than those in group B, with statistically significant differences ($p<0.05$; Figure 1).

Levels of PCT, CRP, and hs-CRP Before and After Treatment in the Two Groups

Levels of serum PCT, CRP, and hs-CRP were compared between the two groups before and after treatment, and there was no significant dif-

Table II. Comparison of results of clinical efficacy between group A and group B [n (%)].

Category [case (%)]	Group A (n=96)	Group B (n=85)	χ^2-value	*p*-value
Significant effect	50 (52.08)	51 (60.00)	0.989	0.320
Effective	19 (19.79)	24 (28.24)	1.775	0.183
Ineffective	27 (28.13)	10 (11.76)	6.827	0.009
Sickness and death	13 (5.32)	4 (4.71)	4.136	0.042
Blood culture turned negative	57 (59.38)	63 (74.12)	3.670	0.055
Total effective rate of treatment	69 (71.87)	75 (88.24)	6.827	0.009

Table III. Comparison of the incidence of toxic and side effects between Group A and Group B [n(%)].

Category	Group A (n=96)	Group B (n=85)	χ^2-value	*p*-value
Nausea and vomiting	4 (4.17)	3 (3.53)	0.049	0.824
Rash	3 (3.13)	4 (4.71)	0.303	0.582
Diarrhea	5 (5.21)	3 (3.53)	0.301	0.583
Phlebitis	2 (2.08)	2 (2.35)	0.015	0.902
Elevated aminotransferase	3 (3.13)	3 (3.53)	0.023	0.879
Total incidence	17 (17.71)	15 (17.65)	0.000	0.991

ference between the two groups before treatment (p>0.05). After treatment, levels of serum CRP, PCT, and hs-CRP in both groups were significantly decreased (p<0.05). As shown in Tables IV to VI and Figure 2, levels of serum CRP, PCT, and hs-CRP in group B decreased more significantly than those in group A (p<0.05).

Discussion

Neonatal septicemia is a clinically common neonatal disease[15], and its incidence has been increasing in recent years[16]. The immune system of newborns is not fully developed, so its immunity is low. After infected with bacteria or viruses,

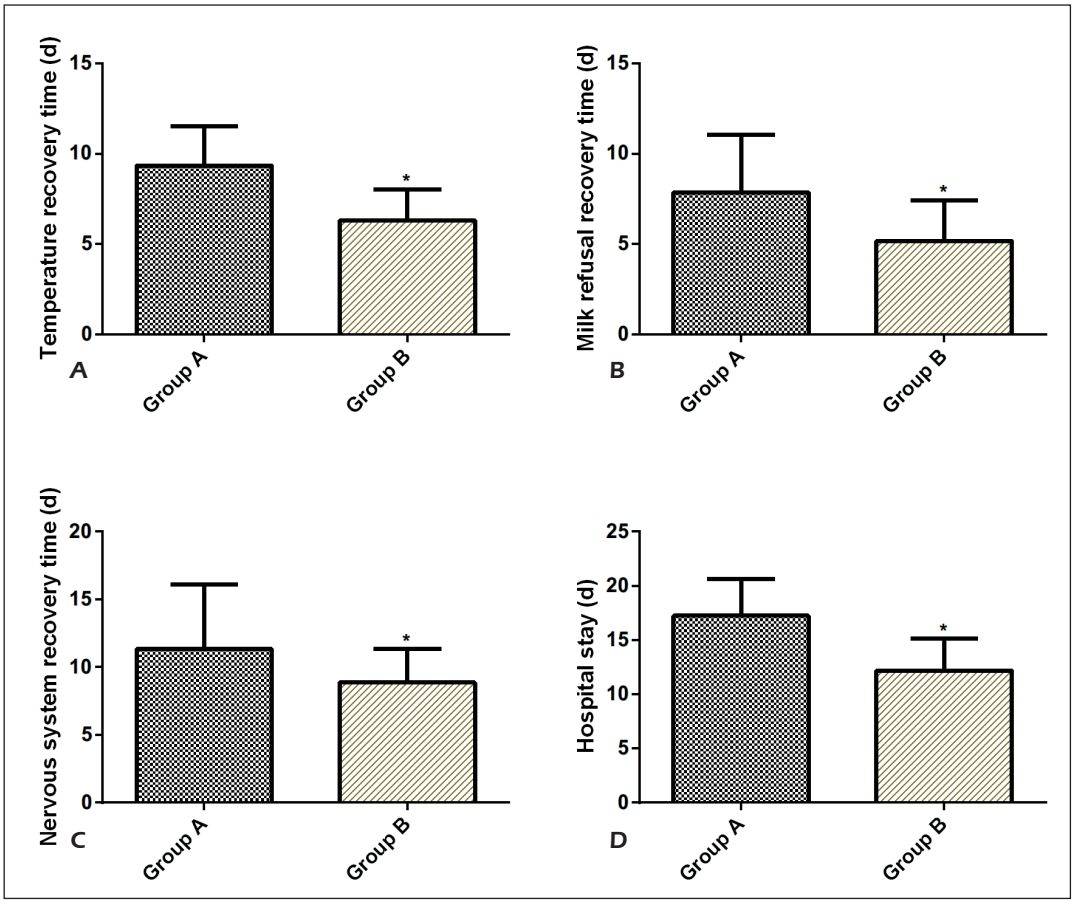

Figure 1. Comparison of hospitalization time and clinical symptoms, such as body temperature, milk rejection, and neurological symptoms in group A and group B. **A**, Comparison of the time of body temperature improvement in group A and group B; the time of body temperature improvement in group A was significantly higher than that in group B (p<0.05). **B**, Comparison of the time to improve milk retention in group A and group B; the time to improve milk retention in group A was significantly higher than that in group B (p<0.05). **C**, Comparison of neurological recovery time in group A and group B; neurological recovery time in group A was significantly higher than that in group B (p <0.05). **D**, Comparison of hospitalization time in group A and group B; the hospitalization time in group A was significantly higher than that in group B (p<0.05). Note: compared with group A, *p<0.05.

Table IV. Comparison of levels of serum PCT before and after treatment between the two groups (x±SD).

Group	PCT (ng/L)			
	Before treatment	After treatment	*t*-value	*p*-value
Group A (n=96)	7.866±4.258	3.643±1.179	8.860	<0.001
Group B (n=85)	7.471±4.387	1.622±0.545	12.230	<0.001
t-value	0.532	<0.001		
p-value	0.626	14.450		

Table V. Comparison of levels of serum CRP before and after treatment between the two groups ($\bar{x}$±SD).

Group	CRP (mg/L)			
	Before treatment	After treatment	*t*-value	*p*-value
Group A (n=96)	26.392±5.115	13.328±4.290	18.500	<0.001
Group B (n=85)	25.824±4.567	9.283±3.915	26.020	<0.001
t-value	0.416	6.417		
p-value	0.816	<0.001		

newborns are prone to extensive inflammatory responses, which can lead to septicemia[17]. Without timely and effective diagnosis and treatment, it is likely to be complicated by pneumonia, meningitis, and other diseases, thus greatly increasing the risk of death[18]. Therefore, it is particularly important to effectively diagnose and treat infants with neonatal septicemia at an early stage to control the development of the disease and reduce its mortality[19].

Cefotaxime can be used as the first choice of antibacterial agents in the third generation of cephalosporins in the neonatal period, with broad antibacterial spectrum and strong antibacterial effect[20]. It is also effective for penicillin and drug-resistant strains of aminoglycoside antibiotics[21]. Vancomycin is a glycoside antimicrobial agent produced by streptomyces, which is highly sensitive to Gram-positive bacterium[22], and there is almost no drug resistance of bacteria. Its main bacteriostatic mechanism is that it blocks the synthesis of bacterial cell walls, and it is a quick-acting antibacterial agent with small adverse reactions, low prevalence of renal toxicity, recovery after drug withdrawal, and high safety[23,24]. Gamma globulin is an immune-enhancer containing an IgG antibody against broad-spectrum antivirus, bacteria or other pathogens. It can play a dual therapeutic role of immune replacement and immune regulation and can rapidly increase the level of IgG in blood after administration. The mechanism of treating septicemia is to affect the binding of microorganisms to target cell receptors[25]. In this study, vancomycin and cefotaxime were respectively combined with gamma globulin to treat neonatal septicemia, and the results showed that the total effective rate of group B was better than that of group A, and the prevalence of adverse reactions and complications in group B was lower than that in group A. This indicates that vancomycin and cefotaxime respectively combined with gamma globulin is a feasible chemotherapy regimen, but cefotaxime combined with gamma globulin may be more effective in the treatment

Table VI. Comparison of levels of serum hs-CRP before and after treatment between the two groups (x±SD).

Group	hs-CRP (mg/L)			
	Before treatment	After treatment	*t*-value	*p*-value
Group A (n=96)	24.264±8.348	6.368±5.067	17.180	<0.001
Group B (n=85)	24.512±5.069	4.190±0.684	36.720	<0.001
t-value	0.251	3.919		
p-value	0.802	<0.001		

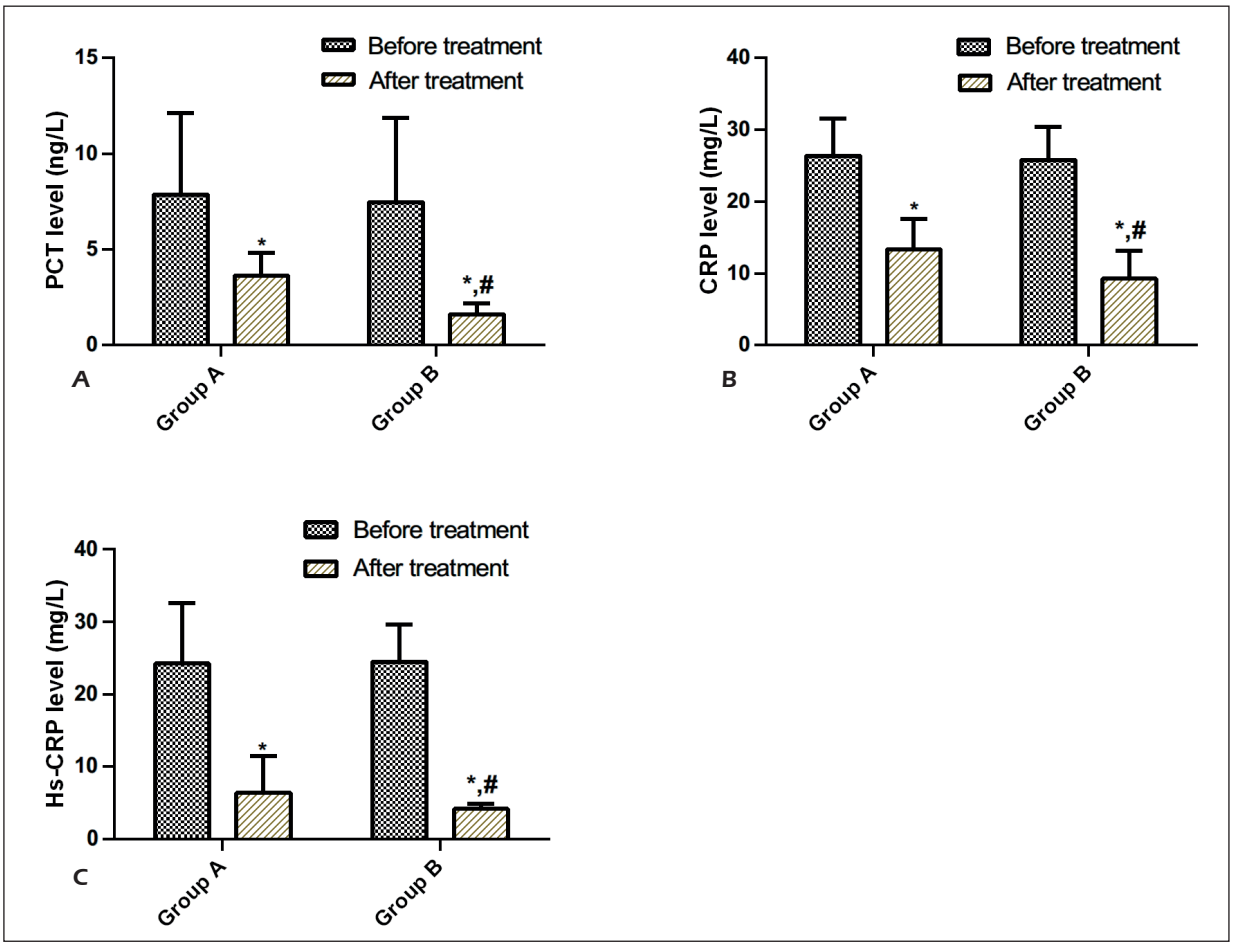

Figure 2. Comparison of levels of serum PCT, CRP, and hs-CRP before and after treatment between Group A and Group B. Comparison of results of serum PCT before and after treatment between group A and group B (**A**): ELISA results showed no significant difference in levels of serum PCT between the two groups before treatment ($p>0.05$); after treatment, levels of blood PCT in both groups decreased significantly ($p<0.05$), and levels of serum PCT in group B decreased more significantly than that in group A ($p<0.05$). Comparison of results of serum CRP between group A and group B before and after treatment (**B**): Results of immuno-scatter turbidimetry showed no significant difference in levels of serum CRP between the two groups before treatment ($p>0.05$); after treatment, levels of serum CRP in both groups decreased significantly ($p<0.05$), and levels of serum CRP in group B decreased more significantly than that in group A ($p<0.05$). Comparison of serum hs-CRP before and after treatment between group A and group B (**C**): Results of immuno-scatter turbidimetry showed no significant difference in level of serum hs-CRP between the two groups before treatment ($p>0.05$); after treatment, levels of serum hs-CRP in both groups decreased significantly ($p<0.05$), and levels of serum hs-CRP in group B decreased more significantly than that in group A ($p<0.05$). Note: compared with pretreatment, *$p<0.05$; compared with group A after treatment, *$p<0.05$.

of neonatal septicemia. Yun and Kim[26] showed that cefotaxime combined with ciprofloxacin has a good effect in the treatment of *Vibrio vulnificus* septicemia. However, Vinh et al[27] revealed that cefotaxime combined with gamma globulin can further reduce the concentration of endotoxin on the basis of rapid sterilization, which is of great significance for the treatment of septicemia. All these suggest that cefotaxime combined with gamma globulin is a feasible and effective treatment for neonatal septicemia.

PCT is a common marker of neonatal infection. The concentration of PCT in the body is increased more significantly in the case of systemic bacterial infection[28]. CRP, an acute infection reactant, plays a very important role in tissue damage repair and inflammation response[29]. Hyper-sensitive C-reactive protein is a new detection technology, which is better, more accurate, and significantly more sensitive than the traditional detection method[30]. At present, there are many studies on the role of PCT, CRP, and hs-CRP in

neonatal septicemia. Fan et al[31] found that hs-CRP and PCT combined with IL-6 had better diagnostic value for early neonatal septicemia. In addition, Kumar et al[32] showed that procalcitonin and CRP may be involved in the occurrence and development of neonatal septicemia, which had a better diagnostic value for neonatal septicemia. However, the role of PCT, CRP, and hs-CRP in the treatment of neonatal septicemia of patients has not been explored before. In this study, levels of expression on serum PCT, CRP and hs-CRP in group A and group B after treatment were significantly decreased compared with those before treatment, while levels of the serum hs-CRP, CRP, and PCT in group B were significantly decreased compared with those in group A. This indicated that cefotaxime combined with gamma globulin in the treatment of neonatal septicemia reduced levels of serum CRP, PCT, and hs-CRP of patients.

Subjects of the study were screened strictly according to the inclusion and exclusion criteria, and there was no significant difference in general clinical baseline data such as gender, days of birth, birth weight, gestational age, and head circumference between groups A and B, ensuring the rigor and reliability of the study. In this research, the regulatory mechanism of vancomycin and cefotaxime combined with gamma globulin on PCT, CRP and hs-CRP has not been clarified; the clinicopathological parameters of patients with neonatal septicemia were different from those of other ages; it has not been discussed whether vancomycin and cefotaxime combined with gamma globulin are suitable for septicemia at other ages, so there are some limitations. In future studies, it is necessary to extend the research time and conduct experiments *in vitro* to further explore the mechanism of action of vancomycin and cefotaxime combined with gamma globulin, respectively in septicemia.

Conclusions

To sum up, vancomycin and cefotaxime combined with gamma globulin respectively can improve the clinical efficacy of patients with neonatal septicemia. Although some adverse reactions occur in the course of treatment, it is within a controllable range. Besides, cefotaxime combined with gamma globulin in the treatment of neonatal septicemia has short improvement time of clinical symptoms, high total effective rate of drugs, low mortality and fewer adverse reactions and complications, and it can also significantly reduce levels of serum CRP, PCT, and hs-CRP, which is worthy of further clinical application.

Conflict of Interests

The authors declare that they have no conflict of interests.

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