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Original Article

Serum sICAM-1 and PCT levels and their prognostic value in neonates with sepsis

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Abstract: Objective: To investigate the changes in serum soluble intercellular adhesion molecule-1 (sICAM-1) and procalcitonin (PCT) levels in neonates with sepsis and their prognostic value. Methods: A total of 153 newborns from May 2017 to March 2018 were selected. Seventy-six children with sepsis were included in the sepsis group, and 77 children without sepsis were included in the control group. The changes in the serum sICAM-1 and PCT levels and related biochemical indicators were quantified before and after treatment for 2 weeks. The risk factors of sepsis neonates were analyzed by a logistics regression analysis. The prognostic value of the sICAM-1 and PCT levels were assessed by receiver operating characteristic (ROC) curves. Results: There were no significant differences in gender, gestational age and weight between the two groups (all P>0.05). The levels of serum interleukin-6 (IL-6), cystatin-C (Cys C), white blood cells (WBC), and C reactive protein (CRP) in the sepsis group were higher than those in the control group (all P<0.05). The serum platelet level in the sepsis group was lower than it was in the control group (P<0.05). The most common bacteria in the sepsis neonates were Escherichia coli (n=21), Staphylococcus saprophyticus (n=16), and Staphylococcus epidermidis (n=16). Serum sICAM-1 and PCT were significantly increased in the pre-treatment sepsis group when compared with their levels in the control group (both P<0.05). Serum sICAM-1 and PCT in the sepsis group after treatment were significantly lower than their levels before treatment (both P<0.05). An ROC curve analysis showed that serum sICAM-1 and PCT had certain diagnostic value for neonates with sepsis. The area under curve (AUC) of sICAM-1 combined with PCT was 0.814, the sensitivity was 78.6%, and the specificity was 87.1%. The efficacy of the combined treatment was significantly higher than the efficacy of the individual indicators, and the difference was statistically significant (P<0.05). Conclusion: Serum sICAM-1 combined with PCT has a high value for the early diagnosis of septic neonates and can be used as a clinical indicator to evaluate the prognosis of children.

Keywords: Neonates with sepsis, intercellular adhesion molecule 1, procalcitonin

Introduction

Neonatal sepsis refers to the invasion of newborns' bloodstreams by pathogenic bacteria. After the bacteria proliferate and release toxins, the children's metabolism is disturbed, and the inflammatory reaction in the children can become rapidly aggravated, eventually leading to septic shock or organ failure in newborns [1]. Neonates with sepsis mainly have clinical symptoms such as abnormal body temperature, apnea, feeding difficulties, and unexplained jaundice. Because of the atypical symptoms of early infection in newborns, they are likely to miss the best treatment time [2]. Therefore, the early diagnosis and treatment of neonatal sepsis has important clinical value. Blood culture is an important diagnostic method for neonatal sepsis, but this method takes a long time and is susceptible to external bacterial contamination, which has a certain interference with the clinical detection effect of the sample [3]. C-reactive protein (CRP) and interleukin-12 (IL-12) can be used as indicators for evaluating neonatal sepsis, but with low clinical specificity and sensitivity [4]. Clinical practice has shown that finding specific diagnostic indicators for neonatal sepsis is beneficial to improving children's treatment outcomes.

Soluble intercellular adhesion molecule 1 (sICAM-1) is a protein factor that mediates the migration of neutrophils to the site of inflammation *in vivo* and has a certain correlation with

the degree of inflammatory response *in vivo* [5]. Procalcitonin (PCT) is a glycoprotein composed of 116 amino acids. In healthy people, the content is very small, but after the patient has a serious infection with a virus or bacteria, macrophages, lymphocytes and some endocrine cells in the body can secrete PCT in large quantities. Kawaza et al. found that the serum PCT of newborns with severe bacterial infections increases significantly, and the abnormal degree of this index can be more sensitive to reflect the degree of infection in the body [6]. This study provides a reference for the clinical treatment of neonatal sepsis by analyzing the changes of serum sICAM-1 and PCT levels in neonates with sepsis.

Materials and methods

Clinical information

A total of 153 newborns were recruited in the Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, from May 2017 to March 2018. Seventy-six cases were sepsis neonates (the sepsis group), including 41 males and 35 females. The gestational age was 37.6±2.7 weeks. Neonates without sepsis were employed as the control group, including 45 males and 32 females (with a gestational age of 37.2±2.1 weeks). The diagnosis of neonatal sepsis refers to the 2016 edition of the *Newborn Diseases Treatment and Treatment Regulations* compiled by the Chinese Medical Association [3]. It mainly includes: (A) blood culture or sterile body cavity culture of pathogenic bacteria; (B) white blood cells (WBC) $<5*10^9$/L; (C) platelet count $\leq100*10^9$/L; and (D) abnormal body temperature. The inclusion criteria were listed as follows: (A) neonatal birth time <28 d; (B) gestational age range is 30.0-40.0 weeks; (C) Apgar score <7. The exclusion criteria were listed as follows: (A) newborns with genetic diseases; (B) newborns with missing or incomplete clinical data; (C) neonates with congenital malformations; (D) abnormalities of the vital organs such as the heart, liver, and kidneys. The relatives of the children gave informed consent and the study was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine.

Treatment methods

According to the clinical characteristics of sepsis neonates, symptomatic treatment is adopted, and mainly includes providing basic nutritional support to children, and to improving acidosis through an intravenous infusion of sodium bicarbonate (CR-Double Crane Pharmaceutical China) at a dose of 4.0 mL/kg. Cerebral edema was treated by an intravenous injection of mannitol (Runbang Pharmaceutical, China) at a dose of 0.4 mg/kg. Nasal continuous positive airway pressure therapy was given to neonates with hypoxemia. An intravenous infusion of vancomycin (Zhejiang Pharmaceutical, China) was employed against infection, 3 times a day, 12.0 mg/time, an an intravenous infusion of gamma globulin was also given to strengthen immunity (Yuanda Shuyang medicine, China), once a day, 800.0 mg/time. The treatment was used continuously for 2 weeks.

Testing index

The cases' basic clinical data were recorded, including gender, gestational age, birth weight, cesarean section, premature rupture of membranes, intrauterine distress, amniotic fluid contamination, and maternal prenatal infection status. A total of 2.0 mL blood was taken from the cases. After standing at 4°C for 1 h, the blood samples were then centrifuged at 1,200 rpm for 30 min, and the serum was collected and stored in a refrigerator at -20°C. Platelets, interleukin-6 (IL-6), cystatin-C (Cys C), white blood cell (WBC) and C-reactive protein (CRP) levels in children were analyzed by an automatic biochemical detector (Beckman, USA). Serum IL-6 and Cys C levels were measured by immunofluorescence.

The sICAM-1 and PCT levels in the serum samples were detected by Elisa. According to the ELISA kit specification (Jianglai Biotechnology, China), the antibody coating solution was added to the 96-well microtiter plate, and the blank well (no standard or sample), the standard wells, and the sample wells were set. Standards and samples were diluted as required, and then added to the corresponding micropores (30.0 μL per well). The plate was shaken evenly and then incubated at 37°C for 20 min. After it was washed 3 times with PBS (5 min/time), 30.0 μL HRP-labeled rabbit anti-human sICAM-1 antibody (1:800), PCT antibody (1:1,200, Abcam, UK) were added and incubated at 37°C for 20 min. Then the plate was washed 3 times with PBS (5 min/time), 10.0 μL of the color developer was added with oscillating and mixed, and

Table 1. Analysis of baseline data of neonates with sepsis

Index	Control group (n=77)	Septic group (n=76)	t/χ^2	P
Gender (male/female)	45/32	41/35	0.314	0.575
Gestational age (week)	37.2±2.1	37.6±2.7	1.098	0.274
Weight (g)	3,462.1±357.6	3,572.8±428.4	1.736	0.085
Platelets ($*10^9$/L)	341.2±32.8	127.6±28.3	43.103	0.000
IL-6 (ng/L)	12.4±0.1	23.2±0.2	421.609	0.000
Cys C (mg/L)	1.3±0.2	2.1±0.3	19.382	0.000
WBC ($*10^9$/L)	10.7±2.4	13.6±2.7	7.024	0.000
CRP (mg/L)	2.3±0.7	26.7±3.8	55.063	0.000
Caesarean section	56	52	0.342	0.559
Premature rupture of membranes	18	24	1.292	0.256
Amniotic fluid pollution	4	27	21.870	0.000
Intrauterine distress	6	13	3.050	0.081
Mother prenatal infection	2	11	6.939	0.008

Note: IL-6, interleukin-6; Cys C, cystatin-C; WBC, white blood cells; CRP, C reactive protein.

Table 2. Distribution of pathogenic bacteria in neonates with sepsis

Index	Number of strains	Composition ratio (%)
Escherichia coli	24	31.6
Staphylococcus aureus	18	23.7
Staphylococcus epidermidis	16	21.1
Klebsiella pneumoniae	7	9.2
Enterococcus faecalis	4	5.3
Escherichia coli	5	6.5
Acinetobacter ruta	2	2.6

then incubated at room temperature for 20 min. Finally, a stop buffer was added to stop the reaction, and then we measured the OD value of each well using a microplate reader at 450 nm.

Outcome measures

The efficacy evaluation criteria were listed as follows: (A) cure: clinical signs disappeared after treatment, normal laboratory tests and biochemical indicators; (B) progress: clinical symptoms of the children are reduced, laboratory tests and biochemical indicators have some improvement; (C) invalid: the clinical symptoms of the children were not improved or were aggravated.

Statistical analysis

SPSS 21.0 software was used for the statistical analysis. The measurement data was expressed as the mean ± standard deviation ($\overline{x}$ ± sd), and conducted with an independent sample t test. The paired sample t test was used for the data of before and after treatment. The count data was expressed as a percentage and compared with χ^2. The prognosis of sepsis in the neonates was treated as a dependent variable. Sex, gestational age, body weight, Cys C, WBC, CRP, IL-6, sICAM-1, PCT, cesarean section, premature rupture of membranes, intrauterine in neonates with sepsis distress, amniotic fluid contamination, and maternal prenatal infection were independent variables. Logistic regression analysis was used to investigate the risk factors of neonates with sepsis. P<0.05 indicated a statistically significant difference.

Results

Clinical features of sepsis neonates

There were no significant differences in gender, gestational age, body weight, cesarean section, premature rupture of membranes, and intrauterine distress between the two groups (all P>0.05). The serum IL-6, Cys C, WBC, and CRP levels in the sepsis group were significantly higher than they were in the control group (all P<0.05). The incidences of amniotic fluid contamination and maternal prenatal infection in the sepsis group were significantly higher than those in the control group (both P<0.05). The serum platelet levels in the sepsis group were significantly lower than they were in the control group (P<0.05). The most common bacteria in sepsis newborns were *Escherichia coli* (n=21), *Staphylococcus saprophyticus* (n=16) and *Staphylococcus epidermidis* (n=16) (**Tables 1**, **2**).

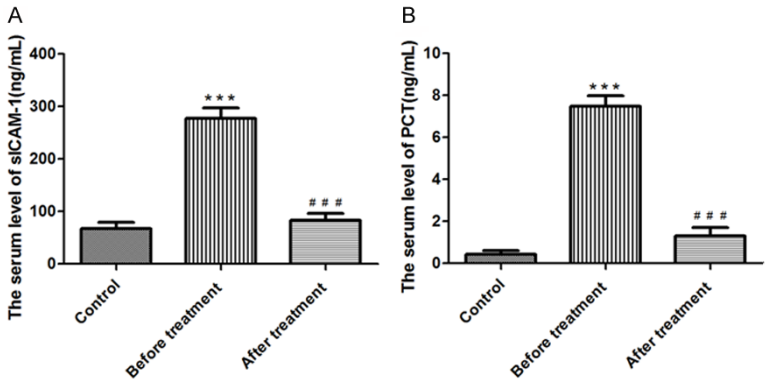

Figure 1. Analysis of serum sICAM-1 and PCT levels in neonates with sepsis Before the treatment in the sepsis group, ***P<0.001 compared with the control group; after treatment in the sepsis group compared with before treatment, ###P<0.001; sICAM-1, soluble intercellular adhesion molecule-1; PCT, procalcitonin.

Table 3. Logistic regression analysis of prognostic risk factors in neonates with sepsis

Index	B	SE	Wald	OR	95% CI	P
Cys C	0.259	0.071	5.462	1.428	1.125-2.317	0.032
sICAM-1	0.547	0.083	6.128	1.795	1.248-2.624	0.026
PCT	0.624	0.067	6.726	1.943	1.286-3.176	0.023

Note: Cys C, cystatin-C; sICAM-1, soluble intercellular adhesion molecule-1; PCT, procalcitonin.

Serum sICAM-1 and PCT levels in neonates with sepsis after treatment

The serum sICAM-1 of the control group was 67.3±12.4 ng/mL, and the serum PCT was 0.4± 0.1 ng/mL. The serum sICAM-1 was 274.2± 64.1 ng/mL, and the serum PCT was 7.6±1.8 ng/mL in the sepsis group before treatment. This result was significantly increased when compared with data from the control group (both P<0.05). The serum sICAM-1 level was 87.4±11.6 ng/mL in the sepsis group after treatment, and the serum PCT level was 1.3± 0.2 ng/mL, both of which were significantly lower than the levels before treatment (both P<0.05, **Figure 1**).

Analysis of risk factors for poor prognosis in neonates with sepsis

Based on the dependent variables (poor prognosis of sepsis in neonates), sex, gestational age, body weight, Cys C, WBC, CRP, IL-6, sICAM-1, PCT, cesarean section, premature rupture of membranes, intrauterine sepsis distress in neonates, amniotic fluid contamination, and maternal prenatal infection were treated as independent variables. A logistic regression analysis showed that Cys C, sICAM-1, and PCT were risk factors for poor prognosis in neonates with sepsis (all P<0.05, **Table 3**).

The diagnostic value of serum sICAM-1 and PCT in neonates with sepsis

An ROC curve analysis found that serum sICAM-1 and PCT have certain diagnostic value for neonates with sepsis. The AUC of sICAM-1 combined with PCT was 0.814, the sensitivity was 78.6%, and the specificity was 87.1%. The combined detection efficiency was significantly higher than the efficiency of the single test (P<0.05, **Table 4** and **Figure 2**).

Discussion

Due to the incompletely developed immune systems of newborns, pathogenic bacteria can invade their blood systems and the newborns are prone to serious diseases of systemic infection, which leads to scurvy. If not treated promptly, the infections may lead to suppurative meningitis and organ failure in children. The infection poses a serious hazard to the child's life [7]. This study found that *Escherichia coli*, *Staphylococcus saprophyticus* and *Staphylococcus epidermidis* were the main pathogens of neonatal bloodstream infection. These types of bacteria have a certain resistance to β-lactam antibiotics; but to carbapenems, the drug is sensitive, which suggests that the type of infectious bacteria in the test can be given a certain reference value for the reasonable selection of drugs before the blood culture and drug sensitivity results. Although current blood culture is the gold standard for detecting sepsis, the method has a long experimental period, complicated operation steps, and a low stability of the test results [8]. The white blood cell count is an important means of diagnosing sepsis, but the diagnostic specificity of this method is not high, which may lead to misdiagnosis [9]. Serum CRP can be used as an indica-

Table 4. Evaluation of the efficacy of sICAM-1 and PCT in detecting neonatal sepsis by ROC curve

Index	AUC	95% CI	Sensitivity (%)	Specificity (%)	P
Cys C	0.654	0.519-0.792	72.3	76.5	0.054
sICAM-1	0.738	0.584-0.837	76.9	82.4	0.031
PCT	0.716	0.561-0.826	74.2	81.7	0.035
sICAM-1+PCT	0.814	0.618-0.926	78.6	87.1	0.027

Note: Cys C, cystatin-C; sICAM-1, soluble intercellular adhesion molecule-1; PCT, procalcitonin.

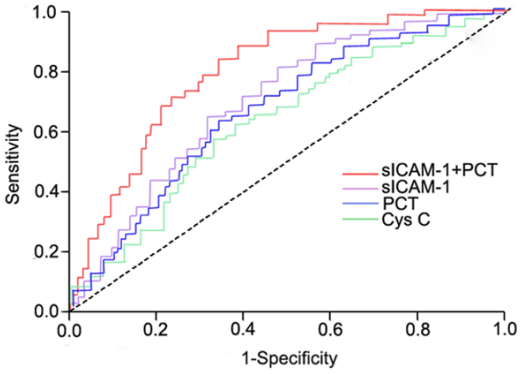

Figure 2. ROC curves of serum sICAM-1, PCT alone and in combination to predict neonatal sepsis. sICAM-1, soluble intercellular adhesion molecule-1; PCT, procalcitonin.

tor to evaluate acute bacterial infection in neonates. However, a study found that serum CRP changes were not obvious in early infection, and the level of infection is increased after severe infection, and the early infection diagnosis of neonates is not effective [10]. Therefore, the search for indicators with higher diagnostic efficacy is of great value in improving the therapeutic effect of neonatal sepsis.

sICAM-1 is a water-soluble form of intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is widely distributed *in vivo* and is a ligand for β2 integrin *in vivo*, mainly located in the cell membranes of macrophages, lymphocytes and vascular endothelial cells. ICAM-1 dissolves after stimulation by external factors, which promotes the increase of serum sICAM-1 level, and it can mediate signal transmission between immune cells and promote the transfer of neutrophils to the inflammation site *in vivo*, thereby aggravating the body inflammatory response [11]. This study found that the serum sICAM-1 level was 87.4±11.6 ng/mL in the post-treatment sepsis group, and the sICAM-1 level was significantly lower than it was before treatment. A study s found that serum sICAM-1 can be significantly increased in early neonatal sepsis, serum sICAM-1 levels decreased significantly after treatment, and sICAM-1 can assess the infection of newborns, which is consistent with this study [12].

PCT is an inflammatory cytokine composed of 116 amino acids with a relative molecular mass of about 13,000. Its gene is located on chromosome 11 of cells *in vivo* [13]. Under normal circumstances, the thyroid parafollicular cells in the body have the function of secreting PCT, but the due to small secretion of this factor, and the poor stability of PCT, the serum PCT rise is not obvious in patients with mild inflammation; after serious infection in the body, except thyroid tissue, macrophages, and lymphocytes in the body can also secrete PCT in large quantities, which promotes the rapid rise of serum PCT levels, which can reflect the degree of infection in the body at an early stage [14]. Studies have found that serum PCT levels increase after bacterial infection in newborns and are positively correlated with the degree of infection in children [15, 16]. This study found that serum PCT was 1.3±0.2 ng/mL after treatment in the post-treatment sepsis group, and serum PCT levels were significantly lower than those before treatment, demonstrating that serum PCT levels are closely related to the severity of sepsis. Ortegón et al. found that patients with adult sepsis have abnormally elevated serum PCT levels before treatment, and PCT levels decrease after treatment, which is consistent with this study [17].

Studies have found that serum sICAM-1, PCT and inflammatory response in patients with sepsis have a certain correlation and can be used as an indicator to assess the degree of infection in patients [18-20]. A logistic regression analysis showed that sICAM-1, PCT, and Cys C were risk factors for poor prognosis in neonates with sepsis. Rohit et al. found that the septicemia with higher serum sICAM-1 levels had a poorer prognosis and a significantly longer treatment cycle [21]. Some studies have found that the clinical prognosis of septic newborns with high serum sICAM-1 and PCT levels is poor, and the clinical symptoms of children are reduced by lowering serum sICAM-1 and PCT levels [22, 23]. This revealed that serum

sICAM-1 and PCT levels can assess the prognosis of neonatal sepsis and provide a reference for improving the clinical outcomes of children. The results of the ROC curve indicated that sICAM-1 and PCT had a better diagnostic efficiency, and the diagnostic power of PCT combined with sICAM-1 was the highest, demonstrating that serum sICAM-1 and PCT have a good diagnostic effects on neonates with sepsis.

This study did not classify sepsis, and the sample size of the sepsis newborns was insufficient, which had a certain impact on the serum sICAM-1, PCT levels and the reliability of pathogen distribution. It is necessary to further expand the sample size in future studies.

In conclusion, serum sICAM-1, PCT can reflect the degree of disease in neonates with sepsis, and the serum sICAM-1 combined with PCT diagnosis has a high reference value for the clinical treatment and prognosis of children. These findings will help determine treatment in neonates with sepsis.

Disclosure of conflict of interest

None.

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