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Original Article

Clinical Application of Serum Inflammatory Factors Combined with Dynamic Detection in the Diagnosis and Treatment of Neonatal Sepsis

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Abstract

Background: To investigate the clinical application value of the combination of the inflammatory factors and dynamic detection in the diagnosis and treatment of neonatal sepsis by detecting serum inflammatory factor C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) levels before and after treatment of neonatal infection.

Methods: A total of 138 neonates with different degrees of infection were randomly enrolled, including 88 cases in the sepsis group and 50 cases in the virus infection group. Another 50 non-infected newborns in the same period were enrolled as the normal control group. Venous blood of all subjects for CRP, PCT, IL-6 detection, and send bacterial blood culture for sepsis and virus infection groups were collected at the same time. In the recovery period, venous blood of children in sepsis group was collected again to review CRP, PCT, IL-6, and differences in each test index of each group were compared.

Results: The serum CRP, PCT, IL-6 levels in the sepsis group were significantly higher than those in the virus infection group (all P <0.05); serum CRP, PCT, IL-6 levels in the sepsis group were significantly lower than before treatment (P <0.05); the sensitivity and accuracy of the combined detection of indicators for the diagnosis of neonatal sepsis were significantly improved.

Conclusion: The inflammatory factors CRP, PCT, and IL-6 are closely related to the occurrence and development of neonatal sepsis. Combined detection can effectively improve the diagnostic accordance rate, which is beneficial to the early diagnosis and early clinical intervention of neonatal sepsis.

Keywords: Sepsis; Newborn; C-reactive protein; Procalcitonin; Interleukin-6; Combined detection

Introduction

Newborns have a weak immune system, and they are vulnerable to bacterial attack. If the infection is not diagnosed and treated in time, they can progress and worsen into sepsis. Neonatal sepsis

is currently one of the main reasons causing neonatal death (1). According to the results of epidemiological investigations (2), sepsis ranks first among the causes of neonatal death.

The onset of sepsis is insidious, lacks specific manifestations at an early stage, and the disease progresses rapidly. It is very easy to secondary to severe complications such as septic shock, multiple organ dysfunction, and diffuse intravascular coagulation (DIC). The rational use of antibiotics is the key to reducing the mortality of neonatal sepsis (3). Blood bacterial culture is still the gold standard for the diagnosis of neonatal sepsis, but bacterial culture takes a long time and the positive rate of culture is low, which cannot provide an early diagnosis basis for neonatal sepsis (4). Therefore, it is particularly important to explore the early predictors of neonatal infection. C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) are inflammatory factors closely related to neonatal bacterial infection.

In this study, CRP, PCT, and IL-6 combined dynamic detection was selected to evaluate its clinical value in early diagnosis, guidance and evaluation of prognosis of neonatal sepsis, with a view to providing a laboratory basis for the early comprehensive prevention and treatment of neonatal sepsis.

Materials and methods

Clinical data

Overall 138 neonates with neonatal infections admitted in the Neonatal Department of the Third People's Hospital of Qingdao, Qingdao, China from Jan 2017 to Dec 2018 were randomly enrolled as the research object. According to the diagnosis of discharge, 88 cases were diagnosed as sepsis (laboratory data showed sepsis or clinical symptoms of sepsis, including 32 cases of positive blood culture), 50 cases of virus infection group (confirmed by virological antibody testing: 17 cases of respiratory syncytial virus infection, 12 cases of adenovirus infection, 21 cases of influenza virus infection), and fifty non-infected newborns at the same time were selected the normal control group. The comparison of the three groups of general information is shown in Table 1.

Table 1: The comparison of the three groups of general information

Groups	*Number of cases*	*Gender (cases)*		*Gestational age (weeks) (x±s)*	*Days of age (days)*	*Weight (g) (x±s)*	*Delivery time(h) (x±s)*	*Delivery way (cases)*	
		Males	*Females*					*Normal labor*	*Cesarean section*
Sepsis group	88	48	40	38.12±0.75	10.32±3.21	3631.45±520.43	41.26±12.35	65	23
Virus infection group	50	27	23	38.25±0.73	11.98±3.42	3652.45±579.43	40.31±13.15	40	10
Normal control group	50	26	24	38.05±0.81	12.91±4.54	3643.27±612.52	41.69±11.98	39	11

Case inclusion criteria (5): ①All meet the diagnostic criteria for neonatal infection; ② Within 28 days of age; ③ The consent of the guardian was obtained and informed consent was voluntarily signed to participate in the study; ④ Complete case information and complete laboratory information. Exclusion criteria: ① patients with organ insufficiency; ② children treated with antibacterial drugs before admission; ③ children who were treated with glucocorticoids before admission; ④ patients who have recently used blood products such as plasma, red blood cells, white blood cells, etc. ⑤ Cannot cooperate with the research; ⑥ Incomplete case information. There were no significant differences in general information such as sex ratio, gestational age, day

age, body weight, delivery time, and delivery mode among the three groups, and they were comparable (P> 0.05).

This study was approved by the Ethics Committee of the Third People's Hospital of Qingdao (LLH: 2016120098). The patients of subjects signed the informed consent.

Methods

After the patient was admitted to the hospital and before medication, venous blood was collected and sent for blood culture, CRP, PCT, IL-6, and viral antibody detection. For blood culture detection, the BacT / ALERT3D blood culture instrument of Merrier Company was used to detect the susceptibility of bacterial positive patients. At the same time, venous blood of normal control group newborns was collected for CRP, PCT, IL-6 detection. PCT was detected by electrochemical luminescence method, using German Roche E601 automatic immunoanalyzer and its supporting reagents; IL-6 and respiratory syncytial virus, adenovirus, and influenza virus antibodies were detected by enzyme-linked immunoassay (ELISA), kits were purchased from Virion-Serion Co., Ltd, Germany, FL-312e full-automatic microplate reader (Bio-Kinetics Instrument Company, USA) was used for measurement. The CRP was determined by Siemens ADVIA2400 rate scattering turbidimetry method, using the original auxiliary reagent, the operating instructions were strictly followed, and the indoor quality control met the requirements. Normal reference values: CRP≤10.00 mg / L, PCT≤0.25 ng / ml, IL-6≤23.00 ng / L. Viral antibody detection used qualitative experiments.

Judgment criteria for test results

The test results obtained were positive for CRP> 10.00 mg / L, positive for PCT> 0.25 / ml, positive for IL-6> 23.00 ng / L, and positive for virus antibody detection was considered abnormal. In the combined test combination, one of the positives was judged positive and all negative were considered as negative. Diagnostic evaluation of each test indicator: test diagnosis results were divided into true positive (a), false positive (b), false negative (c), and true negative (d). Calculation formula: sensitivity = a / (a + c); specificity = d / (d + b); accuracy = (a + d) / (a + b + c + d); positive predictive value = a / (a + b); negative predictive value = d / (d + c).

Statistical methods

SPSS 22.0 (Chicago, IL, USA) statistical software was used for data analysis and processing, t test and χ^2 test. The statistical description of the concentration level of the test data measurement data was expressed as ($x \pm s$), and the comparison between groups was performed using independent sample t test. The comparison of enumeration data rate was by χ^2 test, P<0.05 was considered statistically significant.

Results

The serum CRP, PCT, IL-6 levels in the sepsis group were significantly higher than those in the virus infection group and the normal control group, and the differences were statistically significant (P<0.05); the virus-infected group was not statistically different from the normal control group (Table 2).

Serum CRP, PCT, IL-6 levels in the sepsis group were significantly lower than that before treatment (t = 5.803, 3.322, 3.768, P = 0.001, 0.016, 0.009), and the differences were statistically significant (P <0.05) (Fig. 1).

The sensitivity, accuracy, and negative predictive value of serum CRP, PCT, IL-6 combined detection of three inflammatory indicators in the diagnosis of neonatal sepsis were significantly improved compared with individual tests, and the differences were statistically significant (P <0.05) (Table 3).

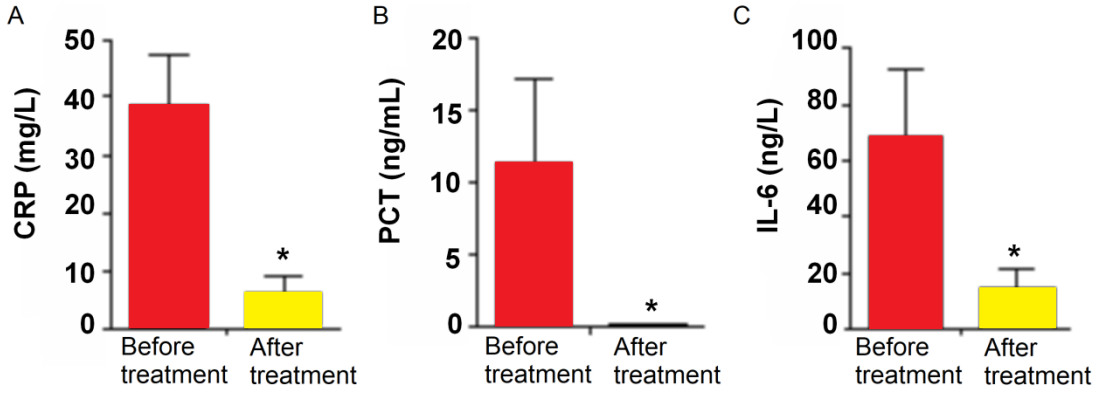

Fig. 1: Comparison of serum CRP, PCT, IL-6 levels before and after treatment in the sepsis group. A. Comparison of serum CRP levels before and after treatment. B. Comparison of serum PCT levels before and after treatment. C. Comparison of serum IL-6 levels before and after treatment. *: P <0.05

Table 2: Comparison of serum CRP, PCT, IL-6 levels in sepsis group, virus infection group and normal control group (x ± s)

Group	*Number of cases*	*CRP (mg/L)*	t	P	*PCT (ng /ml)*	t	P	*IL-6 (ng/L)*	t	P
Sepsis	88	38.69±5.45[a]			11.29±3.67[a]			68.97±15.23[a]		
Virus infection	50	5.69±1.87[b]	6.274	0.001	0.15±0.04[b]	3.325	0.016	15.26±3.73[b]	3.752	0.009
Normal control	50	4.92±1.94	6.395	0.001	0.13±0.05	3.331	0.016	11.42±3.45	4.037	0.007

Note: Compared with virus infection group and normal control group, [a]P <0.05; compared with normal control group, [b]P>0.05

Table 3: Comparison of the value of serum CRP, PCT, LI-6 single and combined detection in diagnosis of neonatal sepsis [% (n)]

Indicator	*Sensitivity*	*Specificity*	*Accuracy*	*Positive predictive value*	*Negative predictive value*
CRP	64.77(57/88)	86.00(43/50)	72.46(100/138)	89.06(57/64)	58.11(43/74)
PCT	72.73(64/88)	88..00(44/50)	78.26(108/138)	91.43(64/70)	64.71(44/68)
LI-6	70.45(62/88)	88.00(44/50)	76.81(106/138)	91.18(62/68)	62.86(44/70)
CRP+PCT+LI-6	98.86(87/88)[c]	84.00(42/50)	93.48(129/138)[c]	91.58(87/95)	97.67(42/43)[c]

Note: Compared with each single test, [c]P <0.05

Discussions

At present, neonatal infectious diseases still rank first in childhood morbidity and mortality, and bacteria and viruses are the most common pathogens (6). There are many causes of neonatal infectious diseases, such as low birth weight of newborns, use of ventilator, operation of deep vein tubes, incomplete implementation of aseptic operations in neonatal intensive care units, and widespread use of antibacterial drugs leading to resistant bacteria increasing (7) will lead to an increase in neonatal infection rates. Neonatal sepsis is the most common cause of death from neonatal infections due to its extremely rapid development (8). Early diagnosis and treatment of neonatal sepsis have important effects on its prognosis. The neonatal system is not well developed, and

the clinical manifestations are often atypical when infection occurs, and there is no complaint. WBC count has been paid much attention to assist in the diagnosis of infectious diseases of the newborn. However, the white blood cell detection is easily affected by internal and external factors, and the fluctuation range is large. It is difficult to make a timely judgment based on the existing WBC count, which delays the timing of treatment. Moreover, some children with bacterial infections are affected by the low immunity of the body, and the changes of WBC count and classification are sometimes not obvious, which cannot provide complete and effective infection information. Therefore, by finding sensitive indicators that can reflect the early infection of newborns, we can fundamentally improve the early diagnosis and treatment of newborn infections and reduce mortality. At present, the application of early inflammatory detection indicators represented by CRP, PCT and IL-6 in neonatal infectious diseases is receiving more and more attention. In the past, procalcitonin and CRP were common clinical indicators (9), but the elevation time in peripheral blood was not as early as IL-6; using CRP and IL-6 for diagnosis, the probability of being affected by other factors is high, and there is a time limit, which also affects the early diagnosis of neonatal infection to a certain extent, and other research results showed that the sensitivity and specificity of these two factors were not ideal in the prediction of neonatal infections(10).

CRP is an acute-phase protein synthesized by hepatocytes. It contains five polypeptide chain subunits, which are non-covalently bonded to form a polymer. It is a globulin and the important sign of the body's inflammatory response. When the body encounters bacterial infection, tissue damage, etc., the body undergoes inflammatory stress, pro-inflammatory cytokines increase, and hepatocytes are stimulated to synthesize CRP. CRP begins to increase in peripheral blood 6-12 h after the inflammation occurs, and its peak value can reach 100-1000 times the normal, because of its short half-life, about 4-6 h, it can be used as an early diagnostic indicator of bacterial infection, which can win time for anti-inflammatory treatment, and it can quickly fall to normal levels after 3-7 days of effective treatment with antibiotics (11). The level of CRP is closely related to the degree of infection and tissue damage, and is not affected by factors such as gender, age, anemia, pregnancy, body temperature, etc. CRP is usually increased after bacterial infection and is not sensitive to viral infection. When the body is infected with virus, the serum content of CRP does not increase significantly. Therefore, CRP can be used as the first diagnostic indicator to identify bacterial or viral infection (12). Serum CRP levels in the sepsis group were significantly different from those in the virus-infected group and the normal control group ($P<0.05$), and CRP levels in the virus infection group were not statistically different from the control group ($P> 0.05$). As an acute phase protein, the content of CRP in the body is affected by many factors (13), and its sensitivity and specificity are low, especially the diagnostic specificity for severe infection is less than PCT. For newborns, the sensitivity of CRP is relatively low due to the short half-life of CRP in vivo, weak liver synthesis ability, and individual differences. The results of this study showed that the sensitivity of CRP to diagnose sepsis was 64.77%, indicating that the value of single detection was limited.

PCT is a peptide composed of 116 amino acids secreted by thyroid C cells, neuroendocrine cells of the lung or intestine. Normal human serum PCT content is extremely low, but when the body is attacked by bacteria, systemic inflammatory response syndrome, sepsis, acute and chronic pneumonia occur, the body produces various proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-6, and IL-8, etc. The secretion of these inflammatory factors promotes the increase of PCT production (14), but PCT does not increase during virus infection, so PCT has become an important indicator for early bacterial infection, especially in the diagnosis of severe infections such as sepsis (15,16). The degree of PCT elevation can reflect the severity of the disease (17). Infection can induce CALC- I ex-

pression and continuous release of PCT in various types of cells in various tissues throughout the body. Under different infections, PCT expression levels are different. When severe bacterial infections occur in newborns (such as sepsis), PCT in peripheral blood rises sharply; when the infection is mild, the PCT content slightly increases. If the infection is effectively controlled, the serum concentration of PCT will gradually decrease, if the PCT concentration remains high, indicating that the treatment effect is not good (18). Therefore, PCT cannot only be used as an indicator of early diagnosis of neonatal bacterial infections. Dynamically detection of its serum level can also be able to monitor the condition and determine the prognosis. After treatment, the serum PCT concentration decreased to a level comparable to that of normal neonatal serum, indicating that the treatment effect and the prognosis is good. The study found that through clinical trials comparing inflammation-related indicators such as PCT, WBC count, and hsCRP, the results showed that the sensitivity and accuracy of serum PCT were higher than WBC count and hsCRP (19). Serum PCT levels in the sepsis group were significantly higher than those in the virus infection group and the normal control group. There was no significant difference between the virus infection group and the normal control group; the sensitivity of PCT to diagnose sepsis was only 72.73%, and PCT levels do not increase in 27.27% of children with sepsis. When the PCT level was not high and the bacterial infection cannot be ruled out clinically, a comprehensive determination should be made in combination with other relevant inspection indicators.

IL-6 is a cytokine with various biological activities; it is a multifunctional protein in defense, acute phase response, immune response and hematopoietic response (20). It can induce liver cells to produce acute phase proteins such as CRP, which appear in the blood circulation earlier than CRP in infectious diseases, so IL-6 can indicate the presence of early infectious diseases earlier than CRP (21). Most normal newborn blood IL-6 levels are extremely low.

During bacterial infection, bacterial lipopolysaccharide and the intermediary substances produced by the infection can stimulate the mononuclear macrophage system and a variety of lymphoid or non-lymphocytes to produce IL-6, causing the IL-6 level to rise rapidly, 2 days before the symptoms appear, IL-6 in blood increased significantly, so IL-6 is considered to be a sensitive and reliable indicator for early diagnosis of neonatal sepsis. The sensitivity of IL-6 reached 89% when the infection occurred, decreased to 67% after 24 h, and 58% after 48 h (22). Verboon-Maciolek et al performed a group comparison study on 111 neonatal infections (75 cases of sepsis and 36 cases of viral infection), and found that IL-6 levels decreased significantly after 2 days of effective antibiotic treatment, which can provide some basis for clinical rational antibiotic use (23). In addition, in children with viral infection, 80% -90% of IL-6 levels are in the normal range, which indicates that IL-6 can be used as an important indicator for diagnosis of sepsis and viral infection. Changes in peripheral blood IL-6 levels are significantly related to prognosis, and high levels of IL-6 can reflect the risk of complications (24). In this study, the expression level of IL-6 in the sepsis group was significantly higher than that in the virus infection group and the normal control group. The sensitivity of IL-6 to diagnose sepsis was 70.45% and the specificity was 88.00%. Although IL-6 has early predictability for the diagnosis of neonatal bacterial infections, the half-life of IL-6 is only a few hours, its peak appears early, and it is maintained in the blood circulation for a short time, so untimely sample collection is prone to negative results. As a result, its value is limited by time, affecting its diagnostic sensitivity.

The results of this study showed that the sensitivity of CRP, PCT, and IL-6 in the detection of neonatal sepsis was 64.77%, 72.73%, and 70.45%, and the accuracy was 72.46%, 78.26%, and 76.81%. The sensitivity of each test was not high and the accuracy was not strong. The combined detection of three indicators for the diagnosis of neonatal sepsis can complement and confirm each other, and the sensitivity and accuracy are significantly improved to 98.86% and 93.48%, respectively. Combined detection is

helpful for early diagnosis and early clinical intervention. Dynamic detection can monitor the condition, guide treatment and evaluate prognosis.

Conclusion

Combined detection of CRP, PCT, and IL-6 could improve the sensitivity and accuracy of diagnosis, and early diagnosis of neonatal sepsis can be used to guide clinical medication and save the lives of children.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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