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Diagnostic value of procalcitomin on pediatric severe infection.

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Abstract

Objective: To observe PCT changes of pediatric severe infection, evaluate relations between its diagnostic value and disease severity conditions.
Methods: This study observed changes of infantile general bacterial infection, local bacterial infection, viral infection and infants without bacterial infection, relevance between disease severity conditions and PCT according to infantile severe evaluation scores.
Results: PCT as bacterial indexes, had statistical differences in body and local bacterial infection (F=1728.67 P<0.0001). PCT had relevance with disease severity conditions in general bacterial infection group (F=2635.98, P<0.0001). But in local bacterial infection group, viral infection group and non-infection group, there were no statistical differences between PCT and disease severity (P>0.05).
Conclusion: PCT can differentiate bacterial infection and non-bacterial infection effectively, especially in general bacterial infection, PCT will increase significantly. With local bacterial infection, PCT will increase slightly.

Keywords: PCT, Infection, Diagnosis, Infantile severe diseases scores.

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Introduction

Infection diseases account for relative high percentage in infantile diseases, which will threat health of children severely. How to judge whether has bacterial infection, severity degree of infection and curative effects are important programs for pediatric clinical doctors. Common clinical infection indexes at present have WBC, N, CR, ESR, ferrintin concentration of peripheral blood, but which lack of specificity [1]. Procalcitonin (PCT) initially described as a marker for infection [2], has emerged as an early, sensitive, and specific indicator of bacterial infection during the last decade [3,4]. PCT is a precursor peptide of the hormone calcitonin and is released from multiple tissues in response to systemic bacterial infections *via* direct stimulation of cytokines [5]. PCT increases promptly within 4 to 6 h upon stimulation and decreases by 50% daily if the systemic bacterial infection is controlled by the immune system and effective antibiotic therapy given the half-life of PCT in the systemic circulation [6,7]. PCT level is elevated in patients with systemic bacterial infections and, unlike other markers, it is usually not elevated in patients with inflammation due to viral infection or non-infectious diseases. Thus, serum PCT has higher diagnostic accuracy for the diagnosis of bacterial infection than standard biochemical parameters, such as the WBC count and serum CRP levels [8-10]. Assicot et al. report that PCT of bacterial infection patients increase, afterwards, it is used by clinic diagnosis gradually. Although PCT was associated with infection, there was less research in severe infections in pediatrics. The purpose of this study is to observe changes of PCT on infantile severe infection, and its relations with disease severity degree, then explore the diagnostic value of PCT on infantile severe infection.

Objects and Methods

Study objects

Experimental group were cone from patients in hospital in ICU of affiliated children's hospital of Nanjing medical university from June, 2012 to April, 2015. The control group were from children with normal outpatient physical check-ups. The age was from 29 d to 14 y old. This study was consented by hospital ethics committee. The number of ethical committees of Nanjing Children's Hospital is 2012006. All inclusive samples were agreed by guardian and entered into study by doctor in charge. The disease severity degree was divided according to infantile severity scores: equal to or less than 70; from 71 to 80; over 80.

Inclusive and exclusive criteria in the observation group: *Inclusive criteria and typing:* First, general bacterial infection group: there were doubted or identified infection caused by bacterial infection, such as positive cultivation, tissue staining, PCR, clinical syndromes related to infection highly, pollution exclusion. Second, local bacterial infection group: local tissue or independent organ infection, the basis of pathogen without dissemination, such as accurate infection in phlegm cultivation, urine cultivation in midpiece segment, stool cultivation, CSF cultivation. Third, viral infection group: viral pathogen

identified by positive cultivation, tissue staining or PCR, such as hand-foot-mouth diseases, viral encephalitis, measles etc., bacterial infection was excluded. Fourth, non-infection group: like infantile patients with closed trauma, intoxication, asphyxia, heat syndrome, patients without any infection history before admitted into PICU, various body fluid cultivations had no abnormality and clinical infection.

Exclusive criteria: First, patients who died within 24 h after admitted into hospital, and cannot receive infection identification. Second, patients who had chronic diseases, malignant tumor, AID, immune-deficiency diseases, hyper-sensitive diseases, inherited metabolic disorders and applied immunosuppressants.

Detection methods

This study collected samples, detect PCT concentration, cultivate tissue, secretion and blood before using anti-bacterial drugs. Doubted viral infection patients were given drug nucleic acid detection and common viral antibody detection. Infantile patients given severe cases scores.

Reagent and instruments miniIDAS automatic immunofluorescence marker

Reagents were VIDASB.R.A.H.M.SPCT. MiniIDAS diagnostic products provided by Shanghai limited company.

Methods

Operation procedures of PCT detection [11]: the methods were to collect 2 ml whole blood of infantile patients, use common coagulant centrifugation and collect 200 μL plasma into fenetra of lath. Then to detect according to miniIDAS automatic immunofluorescence marker. Enzyme Linked Fluorescence Assay (ELFA) technology was applied with the reference value of <0.5 ng/ml.

Statistical management

Statistical analysis used SPSS 13.0 software. All detection results were given bilateral detection, $P<0.05$, there were statistical differences. Measurement results were represented by $\bar{x} \pm s$. Comparison between groups were given single factor ANOVO analysis, if it had statistical differences, would be given SNK-q test.

Results

Sample characteristics of this study

This study included 743 infantile patients, of which, there were 531 cases in experimental group and 212 cases in healthy control group. The age was from 29 d to 14 y old. The average age was 2.74 ± 0.98 y old. Common bacterial infection pathogen included MRSA, *Streptococcus pneumoniae*, *Hemophilus influenza*, pathogenic *Escherichia coli*, coli-aerogenes, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterococcus faecium*, *Acinetobacter baumannii*, *H. pylori*, *Serratia marcescens*, *Burkholderia cepacia* etc. Common viral infection pathogen included coxsackie virus, EV71, Hepatitis B virus, unit-cell virus, adenovirus etc. Other pathogen: mycoplasma, chlamydia and fungus etc.

Comparison results of PCT concentration in different groups seen in Table 1.

Table 1. *Comparison $\bar{x} \pm s$ of PCT concentration in different groups. Notes: Compared with viral infection group and non-infection group; $P<0.05$ in general and local bacterial infection group; general bacterial infection group compared with local bacterial infection group; $P<0.05$. Viral infection group compared with non-infection group; $P>0.05$.*

Groups	Cases	Sex (male/female)	PCT (ng/ml)
Non-infection	109	60/49	0.26 ± 0.18
General bacterial infection	139	72/67	16.77 ± 3.88
Local bacterial infection	159	86/73	4.16 ± 1.53
Viral infection	124	69/55	0.39 ± 0.14
F value			1728.67
P value			<0.0001

Comparison between PCT concentration of general bacterial infection group, local bacterial infection group, viral infection group, non-infection group and disease severity degree seen in Table 2.

Table 2. *Comparison $\bar{x} \pm s$ between PCT concentration of general bacterial infection group, local bacterial infection group, viral infection group, non-infection group and disease severity degree. Notes: General bacterial infection group between groups and compared with the control group, $P<0.05$; local bacterial infection group between groups, $P>0.05$, compared with the control group, $P<0.05$; compared between viral infection group and non-infection group, and compared with the control group, $P>0.05$.*

Diseases severity degree	General bacterial infection group		Local bacterial infection group		Severe viral infection group		Non-infection group	
	Cases	PCT (ng/ml)	Cases	PCT (ng/ml)	Cases	PCT (ng/ml)	Cases	PCT (ng/ml)
The control group	212	0.35 ± 0.09	212	0.35 ± 0.09	212	0.35 ± 0.08	212	0.35 ± 0.08

≤ 70	88	22.8 ± 83.89	67	3.90 ± 1.80	74	0.53 ± 0.14	72	0.29 ± 0.09
71~80	32	19.22 ± 2.64	43	3.62 ± 1.60	36	0.39 ± 0.20	29	0.29 ± 0.08
>80	19	13.71 ± 1.91	49	3.20 ± 1.23	14	0.39 ± 0.13	8	0.32 ± 0.08
F value		2635.98	304.67	46.04	10.88			
P value		<0.0001	<0.0001	<0.0001	<0.0001			

Discussion

Infectious diseases account for 50% in pediatric diseases, which threat health of children severely. With the progress of diagnostic technology, wide application of antibiotics, the infantile infectious diseases change. Pathogen become multiple, complex caused by pathogen. The percentage of mixed infection increase, which bring great difficulty to diagnosis. If we can judge infectious pathogen promptly and accurately, it has great significance for short-term treatment strategies, optimized antibiotics usage and drug resistant prevention production.

PCT is a kind of inflammatory indexes, it produced by thyroid C cells, cannot releases into blood under normal physiological state. Blood in healthy people cannot be detected (<0.1 μg/L). It is thought that it is NSAID, which has great amplification effects of infectious inflammatory reaction. Semi-failure period is from 25 to 30 h. PCT production is regulated by bacterial toxins and multiple inflammatory cellular factors, toxins in bacteria is the main induced stimulation factors. PCT can be detected in 4 h after general infection. PCT increases in 6 h after infection sharply. And it maintains this level from 6 h to 24 h, which is important index of judging early infection. Clinic takes whether has bacteria and infection control as effective reference indexes [12], whether has medical units, even which has been included into one of routine detection items beside bed [13]. The increased PCT has positive relations with bacterial infection severe degree. Clinic can be used to evaluate severe degree of conditions [14]. For judge of condition degree in severe infants, it mainly to give scores by organ function in clinic. PCT introduction provides reliable index for bacterial infection dynamic observation. Results of this study show that general bacterial infection changes with the changes of condition severe degree and PCT concentration. But condition severity changes in local infection group, viral infection group and non-infection group. But PCT has no significant changes, which shows PCT is the only limitation of bacterial infection index. PCT is from 10 to 100 ng/ml in sepsis and pyemia, even higher. Some scholars think that PCT>10 ng/ml is negative in blood cultivation, it should combine with clinic to consider bacterial infection and general inflammatory reaction. Diagnostic specificity of PCT on severe pyemia and pyemic stoke is over 95%. There are reports show that [15], PCT can be new target for pyemia treatment, hamsters with pyemia are injected by PCT can increase its death rate, anti-PCT serum treatment can increase its survival rate.

This study finds that PCT can differentiate bacterial infection and non-bacterial infection effectively, especially there is general bacterial infection, PCT will increase significantly. When there is local bacterial infection, PCT will increase slightly. When there is non-bacterial infection, including no changes of viral infection, trauma, asphyxia, intoxication, arrhythmia etc. But there are studies show that [16] some specific bacteria is infectious, concentration of PCT has no significant changes. This study also observes patients who don't have bacterial infection in some hepatic function injury and blood clean treatment, there are false positive conditions of increased PCT. At present, there are similar reports [17-20]. It still cannot explain this phenomenon. This issue also explore its reasons furtherly.

CRP as one of important markers of sensitive, early diagnostic bacterial infection, which has been applied in clinic. Because of relative low diagnostic bacterial specificity, various inflammations, tissue inflammation, surgical trauma, even some non-infectious inflammatory reaction, such as vomiting, strong excises also increase. CRP increases rapidly stressed by various stimulations. After conditions improve, it decreases rapidly, which bring a certain barriers to sample collection. So it is very little in single diagnosis in clinic for diagnosing bacterial infection. There are clinical doctors find that PCT and CRP in judging bacterial infection can improve diagnostic specificity [21].

For fever patients in clinic, this study is to judge whether has bacterial infection and use antibiotics according to leukocyte number of peripheral cells and its classification results. But leukocyte number of peripheral cells and its classification results influenced by many factors, which have a certain limitation for specificity and sensitivity of bacterial infection diagnosis. Such as tumor, chemotherapy and glucocorticoid etc. all can influence secretion of inflammatory factors and medullary hematopoiesis. But PCT has advantages in this part. Through observing tumor infection infantile patients, it is found that sensitivity of PCT and infectious diagnosis is from 59% to 78%. The specificity is 76%. Positive predictive value is 93%. Negative predictive value is 45%, which are better than traditional leukocyte number and classification of peripheral blood.

At present, in clinic, whether use antibiotics, upgrade, degrade or stop using antibiotics mainly according to first-line doctors, it still has subjective interference factor. Because specificity of common diagnostic indexes, such as WBC, CRP, N etc., are relatively poor, so it is not recommended that parameter above singly for guiding clinical antibiotics application.

Through antibiotics application guided by PCT concentration, it achieves great effects on hospitalized days, economic benefit, dysbacteriosis, bacterial resistance etc.

According to recommend, first, PCT<0.1 ng/ml, we don't advocate using antibiotics; second, 0.1 ng/ml<PCT<0.25 ng/ml, we don't advocate using antibiotics; third, 0.25 ng/ml<PCT<0.5 ng/ml, we advocate using antibiotics; fourth, PCT>0.5 ng/ml, we advocate using antibiotics. So we judge whether has bacterial infection, use antibiotics according to PCT concentration to reduce antibiotics overflow, improve economic burden of patients and lower rate of bacterial drug resistant [22]. With the development of diagnostic technology, some new inflammatory indexes are found, such as soluble TREM-1, soluble urokinase-type plasminogen activator receptor, micro RNA-223. But PCT as one quantitative objective index can reflect changes of bacterial infection patients promptly, which have reference value for early accurate diagnosis, guiding antibiotics indication, evaluating curative effects, changing or stopping antibiotics, shortening unnecessary antibiotics exposure time. In clinical treatment, it is very important for early clinical treatment to detect serum procalcitonin level in patients. Now, in the clinical detection of pathogen research work in hospitals, the serum procalcitonin has been widely used for children with severe infection, detected by serum procalcitonin levels, can be quickly detected within 2 h, to take effective treatment measures. Serum procalcitonin levels in children with locally infected and viral infections will not rise significantly, but their elevated levels are still higher than healthy children. Therefore, dynamic PCT monitor can reduce usage time of antibiotics, optimize antibiotics usage, achieve short-time treatment of severe infection, and reduce patients' treatment cost of antibiotics. At the same time, it can reduce drug-resistance bacteria production, opportunity of cross-resistance, possible rate of antibiotics adverse reaction.

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