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The predictive value of C-reactive protein (CRP) and procalcitonin chemical biomarkers in the premature diagnosis of infection in brain ischemic stroke

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Original Article

Abstract

BACKGROUND: The infections are common complications after the ischemic stroke. The aim of this study was to evaluate the anticipatory value of C-reactive protein (CRP) and procalcitonin (PCT) biomarkers in diagnosis of stroke-induced infection.

METHODS: In the current prospective study, 184 patients with cerebral ischemia were enrolled. Serum samples were obtained from patients. The CRP and PCT, white blood cells (WBCs) and monocytes, and final infections were evaluated.

RESULTS: In the first 72 hours, the analysis for CRP revealed that the sensitivity was 41.60%, the specificity was 100%, positive predictive value (PPV) was 100%, and negative predictive value (NPV) was 82.90%. PCT showed that the sensitivity was 85.41%, the specificity was 98.54%, PPV was 95.34%, and NPV was 95%.

CONCLUSION: According to our findings, the evaluation of CRP and PCT with simultaneous clinical observation could be considered as a good step in start of antibiotic therapy.

KEYWORDS: C-Reactive Protein, Procalcitonin, Infection, Ischemia

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Introduction

In 25-65 percent of the patients, the infection occurs in the first few days after ischemic stroke.[1,2] Pneumonia (the infection of pulmonary parenchyma) and the urinary tract infection (UTI) are the most common infectious complications after the ischemic stroke.[3] It has been stated that increasing the probability of infection during the acute phase of stroke is due to immune suppression.[4] The central nervous system (CNS) adjusts the function of immune system through a complicated path including hypothalamus-pituitary-adrenal axis (HPA axis) and the vague nerve as well as sympathetic nervous system (SNS).[5,6] The results of many studies reveal that there is an independent association between the infection caused by stroke and the poor functional outcome after that.[7-9] Therefore, in case the infection emerges in the incipient stage of the illness, antibiotic treatment is recommended.[10] However, the clinical gold standard method is

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time-consuming for diagnosis and delays the antibiotic treatment. Thus, the simple precise diagnostic markers are required to determine the amount of risk. In the other studies, the C-reactive protein (CRP), white globules, and monocytes were examined as the accepted inflammatory markers regarding their easy and common measurement. Procalcitonin (PCT) is selected to differentiate infection from general inflammation.[11-17] All of these biomarkers are available due to easy and quick interpretation.

The values of blood markers such as white blood cell (WBC), CRP, and monocyte as a predictor of infection resulting from the stroke have not adequately been explored; however, they are assessed routinely after the admission of patients. In a study, the biomarkers like CRP, WBC, monocyte, and PCT were sensitive enough to diagnose the infection caused by stroke, but in another one, they did not have enough sensitivity. Thus, due to lack of evidence we cannot be certain about their role in predicting the infection caused by stroke.[13,14] Approximately, one-third of deaths and serious complications are caused by the subsequent complications especially infection.

The changes of the immune markers and stress, the reduction of human leukocyte antigen–DR isotype (HLA-DR) for instance, or increasing the serum level of catecholamine occur during the incipient stage of stroke and justify the high inclination of these patients to bacterial infection after stroke. It is imagined that these blood markers can predict the occurrence of post-stroke infection to a high extent. Thus, considering the importance of early treatment in patients with stroke, its high incidence, the dramatic infection resulting from that, and taking this point into account that early treatment of these patients has a great influence on their life style and function, in this study we attempt to investigate the predictive value of CRP and PCT chemical biomarkers in the premature diagnosis of the ischemic stroke. First, we are to evaluate the diagnostic value of each biomarker in predicting the incipient phase of infection and then proceed with specifying that which one has a better diagnostic value.

Materials and Methods

This prospective longitudinal study was conducted on the patients explored in the course of January, 2014 to March, 2015. It was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (code number: 458, date: December 24, 2013).

First, the experimental studies were carried out; then the patients were followed-up clinically before manifestation of infection and the relationship between this occurrence and the experimental level of each parameter was measured. The sampling method was non-probable and purposeful. The study was carried out in Razi Hospital in Qaemshahr, Iran, and Bou Ali Sina Hospital in Sari. The inclusion criterion was that all the patients should be afflicted by the acute ischemic stroke (AIS) in the first 72 hours before admission. All of the patients signed a consent form for entrance and 10 cc blood was taken from the patients voluntarily, considering the ethics. Stroke was verified by computed tomography (CT) scan or magnetic resonance imaging (MRI). The neurologic disorder was scored using the rating system of the National Health Center for Stroke. The infection caused by stroke includes every infection in the first 5 days of hospitalization.[13,14] Infection is diagnosed by the standards of the center for disease control (CDC).[15] With regard to the outbreak of the type of infection, they fall into three categories including pneumonia (the infection of pulmonary parenchyma), urinary tract infection (UTI), and other infections. The pneumonia is confirmed when there is at least one of the following criteria (the first or subsequent part): 1. examination of abnormal respiration or pulmonary infiltrates in the chest radiography [chest X-ray (CXR)], 2. productive cough along with purulent sputum, the positive microbial culture from the lower respiratory

tract secretions or the positive blood culture. The diagnosis of UTI is based on the two following cases: the fever ≥ 38 °C, the positive nitrite in the urine sample, leukocyte > 40% in each microliter of urine, and bacteria > 10^4 in a type of pathogen microbe. Other infections are verified if the fever is above 38 °C, WBC is above 11000 in each milliliter or CRP is ≥ 10 m/l, and if the clinical manifestation of infection exists. Determining infection is based on the country's standard protocol. The time of diagnosis depends upon the beginning of clinical manifestations and symptoms that lead to the beginning of diagnostic measurements, as a result, the infection is diagnosed. In order to prevent the entrance of people who had infection before stroke, the patients with the fever of more than 38 degree before admission, those who had infection 3 days before stroke, and people who need mechanical intubation were not allowed in the study. The other excluding criteria included being immunosuppressive and being afflicted by human immunodeficiency virus (HIV) and the other immune system deficiencies. The blood samples were taken at the first 72 hours of hospitalization and after three days to examine WBC, monocyte (Sysmex KX-21N, Kobe, Japan), and the level of CRP and PCT. The amount of CRP was measured by immune turbid metric assay (Pars Azmoon Co., Tehran, Iran). The serum level of PCT was measured using enzyme-linked immunosorbent assay (ELISA) (Kryptor PCT®, BRAHMS, Hennigsdorf, Germany).[16] The statistical analysis was carried out using SPSS software (version 18, SPSS Inc., Chicago, IL, USA). The descriptive statistical indexes such as mean, standard deviation (SD), median, and absolute and relative frequencies depending on distribution were calculated. The difference between the groups was evaluated by Kruskal-Wallis or chi-square tests. In addition, the simple logistic regression test, the measured biomarkers, and the existence of infection were investigated and P-value ≤ 0.0500 was considered as the significant level.

Results

The study consisted of 184 members, among which 108 people (58.7%) were men and 76 people (41.3%) were women. The mean of the age of study members was 68.52 ± 9.48 years. The lowest age was 48 years and the highest was 91 years. All of the patients were examined in terms of being afflicted by infection in the hospitalization process. To sum up, 48 patients (26.1%) afflicted by a kind of infection were specified. 10 patients (4.5%) were afflicted by urine infection among which 7 were women and 3 were men. In investigating the infection of respiratory system, it was revealed that 33 patients were afflicted by the infection. Totally, 5 male patients were afflicted by the other infections. All of the patients were investigated in terms of the number of white globules, monocytes, CRP, and PCT, and after three days the experimental markers were evaluated. Comparing the two durations of the experiment revealed that all of the experimental characteristics had significant statistical distinction (P = 0.0001) (Tables 1-3).

Table 1. Result of laboratory tests in the first 72 hours

Laboratory test	First 72 hours		
	Men Mean ± SD	Women Mean ± SD	Total Mean ± SD
WBC (/µl)	7776.36 ± 1723.33	7143.77 ± 1440.21	7515.07 ± 1638.33
Monocyte	2.45 ± 0.98	2.23 ± 0.88	2.36 ± 0.88
CRP	7.40 ± 4.25	6.32 ± 2.16	6.95 ± 3.58
PCT	465.81 ± 259.12	347.46 ± 176.06	416.93 ± 235.32

WBC: White blood cell; CRP: C-reactive protein; PCT: Procalcitonin; SD: Standard deviation

Table 2. Result of laboratory tests in the second 72 hours

Laboratory test	Next 72 hours		
	Men Mean ± SD	Women Mean ± SD	Total Mean ± SD
WBC	13116.42 ± 6060.83	11577.35 ± 10874.29	12480.72 ± 8397.54
Monocyte	3.25 ± 1.86	2.69 ± 1.29	3.02 ± 1.67
CRP	13.51 ± 10.27	10.71 ± 7.32	12.35 ± 9.25
PCT	1205.74 ± 1202.84	713.77 ± 615.24	1002.53 ± 1000.00

WBC: White blood cell; CRP: C-reactive protein; PCT: Procalcitonin; SD: Standard deviation

Table 3. Results of biomarkers in these cases

Biomarkers		First 72 hours		Next 72 hours	
		Infection		Infection	
		Yes	No	Yes	No
CRP	Positive	20	0	44	126
	Negative	28	136	4	10
PCT	Positive	41	2	47	29
	Negative	7	134	1	107

CRP: C-reactive protein; PCT: Procalcitonin

This study was an attempt to evaluate the predictive value of CRP and PCT. In exploring the patients' CRP in the first 72 hours of admission of irritation, ability of the screening test in the diagnosis of patients was 41.60%, the sensitivity showing the ability of screening in diagnosis of the elderly was 100%, the positive predictive value (PPV) of patients was 100% in the first 72 hours with regard to CRP which represents that all of the infected patients had high CRP and the negative predictive value (NPV), which is the probability of not being infected, was 82.90%. Having been investigated, CRP was 91.60% after three days of admission, sensitivity was 93.15%, the PPV was 81.48%, and the NPV was 96.92%. The investigation of PCT in the first 72 hours of hospitalization revealed that irritation was 85.41%, sensitivity was 98.54%, the PPV was 95.34%, and the NPV was 95.02%. In addition, according to the experiment three days after, the PCT of irritation was 97.91%, sensitivity was 78.67%, the PPV was 61.84%, and the NPV was 99.07%.

Discussion

The results of this study revealed that totally 48 patients (26.1%) were afflicted by one of the infections. It was specified that 10 patients (4.5%) were afflicted by the urine infection and in exploring the respiratory system, it was represented that 33 patients were infected. Totally, 5 male patients were afflicted by the other infections. In this study, it was attempted to evaluate the predictive value of CRP and PCT. Investigating the CRP of the patients in the first 72 hours represented that the admission of irritation was 41.60%, sensitivity was 100%, the PPV was 100%, and the NPV was 82.90%. Investigating PCT in the first 72 hours revealed that sensitivity was 85.41%, specificity was 98.54%, the PPV was 95.34%, and the NPV was 95.02%. In a study carried out by Tian et al. in china, the role of PCT in the cerebral ischemia was investigated. The results revealed that the amount of PCT was significantly higher in the patients with cerebral ischemia than in the control group.[18] As the results of the current study, in the study carried out by Fluri et al., the predictive role of CRP, PCT, and WBC in the creation of infection in stroke was investigated. They examined 383 patients with stroke, 66 of which were afflicted by the post-stroke infection. The results suggested that in the patients with high rate of such factors, the incidence of pneumonia and urine infection was higher in the first 5 days after admission.[19] In the research conducted by Worthmann et al., the role of inflammatory factors in the cerebral ischemia infection was investigated. In their study, they measured the role of inflammatory factors in 56 patients. The results revealed that the incidence of infection after stroke was more in the patients with high inflammatory factors like CRP.[20] The results of Welsh et al.'s study

represented that CRP had a high connection with the occurrence of the serious subsequent complications. They revealed that the CRP biomarker accompanied the complications of stroke independently.[21] In another study carried out by Deng et al., the role of PCT was evaluated in the outcome of cerebral ischemia. In a prospective longitudinal study in which they examined 378 patients, they revealed that PCT in the cerebral ischemia was applicable as a predictive marker in the short-term complications of cerebral ischemia.[22] The study of Wang et al. manifested that in the patients with weaker clinical results and higher mortality, the amount of PCT and the CRP biomarkers was significantly higher. In addition, comparing the PCT and the CRP markers in these patients represented that the amount of PCT in the time of admission had a significant relationship with the clinical results after the release of the patients; however, this finding was not verified in case of CRP.[23] Our research also verified the above-mentioned results, but in our study, the results after releasing from hospital were not evaluated. To confirm the results of this study, in another study carried out by Xie et al., the role of PCT and the CRP biomarkers in the pneumonic survival after stroke was investigated. First, they examined 207 patients with cerebral ischemia, 91 cases of which were afflicted by pneumonia and 39 cases passed away.[24] The irritation and feature of PCT in the diagnosis of pneumonia were 84.6% and 71.2%, respectively. In addition, the amount of PCT and the CRP biomarkers was higher in the infected group. They declared that measuring the inflammatory markers and PCT was useful in the prediction of the cerebral ischemia complications. [24]

Conclusion

This study reveals that the inflammatory factors that appear with the positive or negative biomarkers in the experiments, have a determining role in the prognosis of patients afflicted by the cerebral ischemic stroke, and maybe in the future, with regard to this effect, we can help the patients recover through applying new therapeutic strategies. However, considering the convenience and the speed of the experiment, it can be used as a part of tools of checking sepsis. Measuring the level of CRP and PCT along with a proper clinical evaluation can be a guide for antibiotic treatment and can enhance the patients' pre-consciousness. In case of using this test, both the strengths and weaknesses of these biomarkers should be taken into account for making decision. Measuring the serum level of PCT with acceptable irritation and feature can help antibiotic treatment, but it cannot be used as the only diagnostic marker and replaced by the clinical judgment of the physician. The researchers of this study support the measuring value of the level of CRP and PCT as a part of investigating diagnosis; and to reach more certain results, they consider conducting more research in this area necessary.

Conflict of Interests

Authors have no conflict of interests.

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