Research Paper

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"Evaluation of Diagnostic Biomarkers of Bacterial Infection in Febrile Patients of Kathmandu Valley"

Medical Science

KEYWORDS : Procalcitonin, C-reactive protein, fever and infection.

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ABSTRACT

Fever is one of the most frequent causes for hospitalization in developing countries. While several aetiological causes result in a febrile illness, bacterial infections constitute an important "curable" cause of fever. Systemic bacterial infection, bacterial sepsis and related syndromes are life-threatening illnesses that need early initiation of appropriate antimicrobial therapy. Our aim to evaluate the detection of PCT, CRP and IL-6 may be a better combination to identify early bacterial infection in febrile patients. We conclude that the PCT may be a valuable biomarker of bacterial infections in febrile patients, with greater predictive value than CRP and other biomarkers of infection.

Introduction:

Fever is one of the most frequent causes for hospitalization in developing countries. As Kathmandu valley is the capital city so here is so much population and pollution, And also the major fact is changing climate. In this climate many bacteria or organism get better environment to grow and divide. So mostly people got different types of diseases with septicaemia and the most common is febrile fever. While several aetiological causes result in a febrile illness, bacterial infections constitute an important "curable" cause of fever. Systemic bacterial infection, bacterial sepsis and related syndromes are life-threatening illnesses that need early initiation of appropriate antimicrobial therapy.Promp identification of early bacterial infection in fever is very important, since appropriate aetiological treatment and avoidance of unnecessary antimicrobial therapy could not only reduce the morbidity, mortality and costs to patients, but also can reduce the emergence of antibiotic-resistant bacteria. The traditional diagnostic tools, such as leukocyte count,erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are not specific enough for differentiating bacterial infections from viral infections and systemic inflammation.[1,2] Microbiologic culture requires at least 24-48 h, and negative cultures do not exclude the presence of infection.[3] Moreover, only 5-10 per cent of blood cultures performed in hospitals show microorganisms.[4] Therefore, there is an obvious need for more specific biomarkers of bacterial infections in febrile patients.

Procalcitonin (PCT) is the precursor molecule of the calcium regulating hormone calcitonin, consisting of 116 amino acids and encoded by the CALC-1 gene on chro- mosome 11.[5]Procalcitonin (PCT), the precursor of the hormone calcitonin, is produced by C-cells of the thyroid gland or neuroendocrine cells in the lung or intestine[6], and its level in blood of healthy people is less than 0.01 ng/ml. Levels of PCT rise dramatically during bacterial infections, whereas low levels were detected during viral infections or non-infectious febrile conditions.[7,8] Many studies showed the diagnostic property of PCT superior to CRP6,.[9-11] Despite many studies, it remains unclear whether PCT adds significantly to the discriminative properties of the already used set of diagnostic biomarkers, and further studies need to be done to determine the specific diagnostic cut-off value. though the negative cut-off value for PCT is generally believed to be < 0.5 ng/ml, it is not consistant since "negative" PCT value has been observed in some patients with bacterial infection.[12] Interleukin-6 (IL-6) is an important proinflammatory cytokine in the early phase of inflammation, which increases in local and blood circulation after stimulus such as infection, surgery and trauma.[13]CRP is a sensitive index for early inflammatory disease.[14]our aim to evaluate the detection of PCT, CRP and IL-6 may be a better combination to identify early bacterial infection in febrile patients.

Material and Methods:

This study was conducted in the Department of Pathology & Central Laboratory, Kathmandu National Medical College Teaching Hospital,Ghatekullo, Kathmandu, Nepal. The patients were categorized into three groups according to the final diagnosis. The patients with bacterial infection were divided into two groups (A & B) according to the result of blood culture. Group A represented patients with bacteraemia defined by a positive blood culture. Group B represented patients with bacterial infections but with negative blood culture. The patients in group C had no bacterial infection. The samples were collected from all the 105 febrile patients during the period from September, 2013 to October, 2014 andthe routine laboratory measurements were performed.Data were analyzed by SPSS student t-test and one way ANOVA. A P-value <0.05 was considered statistically significant.

Results and Dicussion:

This present study was enrolled total hundred five febrile patients. Demographic and laboratory characteristics of patients with fever in this study are listed in (Table-1). Bacteraemia was confirmed in 28 patients (26.66%), bacterial infection was excluded in 22 patients (20.95%). The final diagnoses are shown in Table 2, most common diagnosis was bacterial pneumonia (42.16%). There were significant differences in the levels of PCT, CRP and IL-6 among the three groups ($P < 0.0001$) (Table-I). The correlation between PCT and CRP was moderate ($r = 0.510$), and those between PCT and IL-6 ($r = 0.401$) were weak. The PCT levels in Gram-positive and Gram-negative bacterial infections were 0.51ng/ml and 2.01 ng/ml, respectively, with the levels significantly higher in gram-negative bacterial infections ($P < 0.05$).

Table I. characteristics of patients (n=105) with fever:

Variables	Group A(N=28)	Group B(N=55)	Group C(N=22)
Sex (M:F)	18:10	32:23	14:8
Age (yr) (Mean ± SD)	43.78 ± 16.11	46.26 ± 47.62	41.02 ± 13.01
Procalcitonin (PCT) (ng/ml)	4.12	0.37	0.15
C-reactive protein (CRP) (mg/l)	131.01	89.50	33.70
Interleukin-6 (IL-6) (pg/ml)	75.16	45.39	25.02

Group A: Bacteraemia; Group B: Bacterial infection with negative blood culture;

Group C: Non-bacterial infections; *P*<0.05, PCT, CRP, IL-6. Significant difference among groups;

Table 2: Diagnosis of enrolled patients (n=105) with fever

Bacterial infection groups (A and B)		Non-Bacterial infection group (C)	
Diagnosis	Number	Diagnosis	Number
typhoid fever	23	Adult still's disease	09
Nasosinuitis	07	Jaundice	05
Bacterial pneumonia	21	Hepaitits E	01
Bacterial gastroenteritis	08	Hepaitits B	04
Urinary tract infection	19	Viral respiratory tract infection	01
Tuberculosis	04	Lymphoma	01
Infectious arthritis	01	Arthritis	01
total	83		22

Table 3: Differences of PCT, CRP and IL-6 concentrations based on gram-positive and gram -negative bacterial infections

Variables	Gram (+ve)	Gram(-ve)
Procalcitonin (PCT) (ng/ml)	0.51	2.01
C-reactive protein (CRP) (mg/l)	109.52	111.49
Interleukin-6 (IL-6) (pg/ml)	62.71	47.52

P<0.05 compared to gram-positive

Table 4: The best cut-off values for procalcitonin, C-reactive protein,interleukin-6, to detect bacterial infection from febrile patients in the infectious diseases department

Biomarker	Cut-off value	Sensitivity (%)	Specificity (%)
Procalcitonin (PCT) (ng/ml)	0.26	64.50	84.00
C-reactive protein (CRP) (mg/l)	73.80	62.00	72.00
Interleukin-6 (IL-6) (pg/ml)	37.67	59.10	70.00

We suggested PCT as a valuable biomarker in detecting bacterial infection in febrile patients. This observation is consistent with the findings of previous researches7,9-11and may be explained by the fact that interferon-gamma (IFN-γ) inhibits IL-1 beta-induced calcitonin mRNA expression and PCT secretion, so serum PCT levels increase less in viral infections as compared with bacterial infections.15 Besides, CRP and IL-6 were also found to be of value in detecting bacterial infection in febrile patients. previous studies have also used CRP level to identify bacterial infections in febrile patients16,17and PCT was superior to CRP in identifying bacterial infection.7,9-11 Though CRP is the most commonly measured acute parameter in infection and sepsis, it is not a reliable marker in identifying bacterial infection because of its low sensitivity and specificity. IL-6 has the same initial kinetics as CRP in the acute phase response. A previous study showed IL-6 as a better prognostic marker of bacterial infection than CRP in patients with febrile neutropenia.18This inconsistency may be due to different testing time. In addition, there was no significant association between PCT and CRP or IL-6, which also might be related to the different peak time and plasma half-life of different biomarkers after a stimulus. In bacterial infections, IL-6 levels rise 2h after endotoxin administration, and then gradually decline.19 PCT is probably synthesized in the liver or monocytes, in response to cytokines such as IL-6 and TNF-α.20,21 PCT increases in blood six hours after a stimulus, reaches a plateau between 12 and 48 h, and then decreases if the stimulus stops. CRP increased four hours later than PCT.8 In general, biomarker measurement has some disadvantages. Probably the combination of biomarkers would lead to a better sensitivity and specificity to predict bacterial infections.

Our study showed that PCT levels in Gram-negative bacterial infections were significantly higher than that in Gram-positive bacterial infections, consistent with results of previous studies.21,22 The TNF-α plays a pivotal role in the cytokine response to Gram-negative bacteria, and also in the release of PCT from various cells in bacterial infection.21 Previous experiment showed that PCT peak value was significantly higher in rats stimulated with lipopolysaccharide (LPS), a component of the outer membrane of the Gram-negative bacteria, than in those stimulated with muramyl dipeptide, a component of the outer membrane of the Gram-positive bacteria.23 Therefore, the PCT level was possibly related to the characteristics of the pathogen.

Conclusion:

These findings suggest that, the PCT may be a valuable biomarker of bacterial infections in febrile patients, with greater predictive value than CRP and IL-6. More prospective and large scale studies are needed to better define the usefulness of PCT in identifying the causes of fever and guiding the rational use of antibiotics. As pointed out above, substantial heterogeneity was evident in quality appraisal both regarding study design, definitions of reference standard and patient population.

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