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Opinion paper

Procalcitonin as a potential predicting factor for prognosis in bacterial meningitis

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ABSTRACT

We investigated the potential role of serum procalcitonin in differentiating bacterial meningitis from viral meningitis, and in predicting the prognosis in patients with bacterial meningitis. This was a retrospective study of 80 patients with bacterial meningitis (13 patients died). In addition, 58 patients with viral meningitis were included as the disease control groups for comparison. The serum procalcitonin level was measured in all patients at admission. Differences in demographic and laboratory data, including the procalcitonin level, were analyzed between the groups. We used the mortality rate during hospitalization as a marker of prognosis in patients with bacterial meningitis. Multiple logistic regression analysis showed that high serum levels of procalcitonin (>0.12 ng/mL) were an independently significant variable for differentiating bacterial meningitis from viral meningitis. The risk of having bacterial meningitis with high serum levels of procalcitonin was at least 6 times higher than the risk of having viral meningitis (OR = 6.76, 95% CI: 1.84–24.90, $p = 0.004$). In addition, we found that high levels of procalcitonin (>7.26 ng/mL) in the blood were an independently significant predictor for death in patients with bacterial meningitis. The risk of death in patients with bacterial meningitis with high serum levels of procalcitonin may be at least 9 times higher than those without death (OR = 9.09, 95% CI: 1.74–47.12, $p = 0.016$). We found that serum procalcitonin is a useful marker for differentiating bacterial meningitis from viral meningitis, and it is also a potential predicting factor for prognosis in patients with bacterial meningitis.

1. Introduction

Bacterial meningitis has high morbidity and mortality worldwide, with 1.2 million cases per year, resulting in 135,000 deaths [1]. The mortality rate of acute bacterial meningitis and the frequency of neurologic sequelae are especially high when the diagnosis and antibiotic administration are delayed [2,3]. The previous studies have demonstrated that patients with a low Glasgow Coma Scale (GCS) at the initiation of antibiotic therapy, low thrombocyte counts, old age, pneumonia, heart failure and seizures after therapy have a high mortality rate in acute bacterial meningitis [4,5].

Procalcitonin (PCT) is a precursor of calcitonin consisting of 116 amino acids [6]. PCT is usually secreted by the thyroid gland, and trace amounts of PCT can be measured in the blood in healthy subjects [6]. However, expression of the CALC1 gene, which makes PCT, is rapidly increased by the stimulation of inflammatory cytokines in an infectious condition [6]. In the infectious condition, the PCT is largely secreted from the thyroid gland as well as the spleen, liver and kidney, and it is rapidly secreted into the blood [7,8]. There is much evidence that the serum PCT is a useful biomarker distinguishing a bacterial infection from a viral infection [9–13]. A previous study has demonstrated that the serum PCT assay is a highly accurate and powerful test for rapidly differentiating between bacterial and viral meningitis in children [12,13]. The serum PCT also differentiates between bacterial infections and viral infections more effectively than the C-reactive protein (CRP) in children with lower respiratory tract infections [10]. In addition, the serum PCT could predict the severity of the disease and the prognosis in patients with pneumonia [9]. Moreover, the

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serum PCT levels are increased significantly in children with febrile urinary tract infections when renal parenchymal involvement is present, and allowed for the prediction of patients at risk of severe renal lesions [14]. These findings suggest that the serum PCT is very useful for clinical practice in various infectious diseases. However, to our knowledge, no comprehensive study to assess the potential role of serum PCT predicting the prognosis in adult patients with bacterial meningitis has been available until now.

Therefore, we investigated the potential role of serum PCT in differentiating bacterial meningitis from viral meningitis, and in predicting the prognosis in patients with bacterial meningitis.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board at our institution. This was a retrospective study of patients with a clinical suspicion of bacterial meningitis admitted to the Neurology Departments of two tertiary hospitals in Busan, Korea from January 2009 to May 2016. All patients had typical clinical histories and laboratory findings of bacterial meningitis. In addition, all patients admitted to centers with a clinical suspicion of viral meningitis during the same period were included as the disease control group for comparisons.

The inclusion criteria of the patients with bacterial meningitis were having (1) clinical features, such as a headache, fever, and signs of meningeal irritation; (2) positive cerebrospinal fluid (CSF) findings, including pleocytosis ($\geqslant$5 mm^3, mainly neutrophilic), elevated protein concentrations ($\geqslant$45 mg/dL), and a reduced ratio of CSF glucose to serum glucose ($\leqslant$0.60); (3) a negative CSF stain, culture, or polymerase chain reaction (PCR) for viruses, mycobacteria, and fungi; and (4) a positive CSF culture, smear, or PCR for bacterial pathogens or a good specific response to anti-bacterial therapy [15]. We defined viral meningitis based on a combination of the clinical history and laboratory findings. These included (1) clinical features, such as the acute onset of headache, fever, and signs of meningeal irritation; (2) positive CSF findings, including pleocytosis ($\geqslant$5 mm^3, mainly lymphocytic), normal or slightly elevated protein concentrations ($\geqslant$45 mg/dL), normal ratio of CSF glucose to serum glucose ($\leqslant$0.60); and (3) a negative CSF stain, culture, or PCR for bacteria, mycobacteria, and fungi [15]. We excluded patients who did not have an assessment of their blood procalcitonin levels.

A total of 80 patients with bacterial meningitis met the inclusion criteria for this study. In addition, we included 58 patients with viral meningitis as disease control groups. Of the 80 patients with bacterial meningitis, 13 patients expired during hospitalization. Of the 80 patients with bacterial meningitis, 47 had a positive CSF culture, smear, or PCR for bacterial pathogens, comprising 24 with *Streptococcus* species, 8 with *Staphylococcus* species, 6 with *Klebsiella* species, 5 with *Listeria* species, and 4 with other species. Of the 58 patients with viral meningitis, 25 with viral pathogens were identified using PCR of the CSF, comprising 16 with enterovirus, 5 with herpes simplex virus, 3 with herpes zoster virus, and 1 with Epstein-Barr virus.

2.2. Measurements

Initially, we analyzed the diagnostic value of serum PCT in distinguishing bacterial meningitis from viral meningitis. In addition, we investigated the potential value of serum PCT in predicting the prognosis in patients with bacterial meningitis. We used the mortality rate during hospitalization as a Smarker of prognosis in patients with bacterial meningitis. Thus, we divided the patients with bacterial meningitis into two groups: with and without death. The differences between the groups were analyzed using demographic profiles including sex, age, and diabetes mellitus (DM), blood profiles including white blood cells (WBCs), platelet, CRP, and PCT, CSF profiles including WBCs, protein, and glucose ratio (CSF/blood), and clinical profiles including systolic and diastolic blood pressure, heart rate, the GCS at the time of admission, and death as independent variables. We analyzed the blood, CSF, and clinical profiles that were obtained on the day of admission. The serum PCT concentrations were measured using an electrical chemiluminescence assay (cobas e 411, Roche Diagnostics, Indianapolis, IN, USA), and the measuring range was 0.05–200 ng/mL.

2.3. Statistical analysis

Comparisons were analyzed using Chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney U-test for numerical variables. Categorical variables were presented as the frequency and percentage. Numerical variables with normal distribution were presented as the mean ± standard deviation (SD), and those without normal distribution were described as the median with range. In addition, separate bivariate logistic regression models for each tool were used to determine the odds ratio in predicting bacterial meningitis and death. To perform multivariate analyses and evaluate the sensitivity and specificity for predicting bacterial meningitis and death, we analyzed the clear cutoff values with the Receiver Operating Characteristic curve (ROC). Continuous variables were converted into categorical variables by dichotomizing them in accordance with the clear cutoff values in the logistic regression analysis. The statistically significant *p*-value was set to <0.05. All statistical tests were performed using MedCalc® (MedCalc Software version 13, Ostend, Belgium).

3. Results

3.1. Differences in measurements between patients with bacterial and viral meningitis

Table 1 shows a comparison of the demographic and laboratory profiles between the patients with bacterial and viral meningitis. The demographic profiles including age and DM; the blood profiles including WBCs, platelet, CRP, and PCT; the CSF profiles including WBCs, protein, and glucose ratio; and the clinical profiles including GCS and death were significantly different between the patients with bacterial and viral meningitis. The best cut-offs for predicting bacterial meningitis were 39 years in age, 12,310 $\times$ 10^6/L in WBCs of blood, 0.12 ng/mL in PCT, 800/mm^3 in WBCs of CSF, and 15 in GCS, respectively. Multiple logistic regression analysis showed that old age, high levels of WBCs and PCT in the blood, high levels of WBCs in the CSF, and low levels of GCS were independently significant variables for predicting bacterial meningitis (Table 2). The risk of having bacterial meningitis with high serum levels of PCT (>0.12 ng/mL) was at least 6 times higher than the risk of having viral meningitis (OR = 6.76, 95% CI: 1.84–24.90, p = 0.004). The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive values, and negative predictive values of PCT for predicting bacterial meningitis were 88.75%, 74.14%, 3.43, 0.15, 82.56%, and 82.69%, respectively.

3.2. Differences in measurements between bacterial meningitis patients with and without death

Of the 80 patients with bacterial meningitis, 13 patients died during hospitalization. The demographic profiles, including age and DM, the blood profile including PCT, and the clinical profiles including GCS, were significantly different between the patients