Interleukin-10 serum level in acute coronary syndrome patients

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Abstract

Aim To compare plasma IL-10 concentrations in patients with Acute Coronary Syndrome (ACS) with those in Coronary Artery Disease (CAD).

Methods ACS patients hospitalized in intensive coronary care unit (ICCU) of Cipto Mangunkusumo Hospital/Faculty of Medicine University of Indonesia (CMH/FMUI), Persahabatan Hospital, MMC Hospital, and Medistra Hospital, Jakarta, between May 2005 and May 2006, were included in this study. The ambulatory CAD patients were taken as comparator. The serum IL-10 level was measured by immunoassay method, and compared by using Independent Student’s t-test. To investigate whether IL-10 serum level could predict ACS, the sensitivity and specificity of this parameter towards SKA in various IL-10 serum levels were calculated as well.

Results In this observational study, as many as 146 subjects were analyzed, consisting of 84 ACS patients, and 62 coronary artery disease (CAD). The IL-10 level was higher in the group of ACS patients (7.37 pg/mL + 7.81, CI 95% 5.68-9.07) than that in CAD patients (1.59 pg/mL +1.55, CI 95% 1.2-1.98). The optimal cut-off point for serum IL-10 level is >1.95 pg/mL, with 79.76 % sensitivity and 77.42 % specificity.

Conclusion The IL-10 level was higher in the ACS patients compared to that in CAD patients. Serum IL-10 measurement is a quite superior method to distinguish acute and stable condition, eventhough it is not as good as hsCRP for the same purpose. (Med J Indones 2009;18:167-71)

Key words: Interleukin-10, acute coronary syndrome

Previous studies have shown that in the acute coronary syndrome (ACS), proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are released from macrophages and T lymphocytes. These cytokines then stimulate the acute phase reactant, C- reactive protein (CRP) in the liver.1

Accumulating evidence showed a role of the immunoregulatory, antiinflammatory cytokine interleukin-10 (IL-10) in the aetiology of ACS.2,3 Interleukin-10 (IL-10), a strong antiinflammatory cytokine, is secreted by Th2 subtype lymphocyte and most macrophages. It is known to inhibit many cellular processes and might have important roles in plaque progression, rupture, or thrombosis, including activation of NF-κB,4 metaloproteinase production,5 tissue factor,6 cyclo-oxygenase expression,7 and cell death.8

In patients with ACS, low admission levels of IL-10 have been associated with an increased risk of cardiovascular events and high IL-10 levels with a decreased risk.9,10 However, recent study showed conflicting results.3
This study aimed to compare plasma IL-10 concentrations in patients with ACS with those in CAD subjects.

METHODS

This present study investigated, in a cross-sectional format, whether the bodily acute and chronic proinflammatory response as shown in the alteration of serum IL-10 level in ACS patients is different from those with coronary heart disease (CHD).

Subject

All ACS patients hospitalized in intensive coronary care unit (ICCU) in Cipto Mangunkusumo Hospital / Faculty of Medicine University of Indonesia (CMH/FMUI), Persahabatan Hospital, MMC Hospital, Medistra Hospital were recruited for the study by consecutive sampling. Age and gender matched CHD patients visited the Cardiology Outpatient Clinic Department of Internal Medicine CMH/FMUI and Integrated Cardiac Service Outpatient Clinic CMH were recruited as control by consecutive sampling method as well. All patients in both groups fulfilling the inclusion criteria and without exclusion criteria, who gave informed consent after receiving explanation from the investigators, were enrolled as study subjects. The study was carried out between May 2005 and May 2006. All procedures in this study had been approved by the FMUI Research Ethics Committee.

Inclusion and Exclusion Criteria

ACS patients admitted to study centers mentioned above, fulfilling the ACS criteria that occurs not earlier than 72 hours from recruitment time were included in this study. CHD patients visiting study centers mentioned above and willing to participate were taken as comparator group.

The following patients were excluded from the study: currently in acute or chronic infection, patients with inflammatory response disorders such as autoimmune disease, connective tissue disease, neoplasm, trauma or surgery within 1 month prior to recruitment, currently receiving corticosteroid, NSAID, or immunosuppressive therapy, statin therapy in CHD group. In ACS group, statin is only given after collection of blood sample for measurements of inflammatory response (for observational study). Patients receiving thiazolidindione therapy, patients with chronic kidney or liver disease were also excluded.

Observed Parameters / Variables

History taking includes age, gender, education level, ethnic groups, history of previous chest pain and myocardial infarction, smoking habit, medication history, history of hypertension, history of DM, history of dyslipidemia, family history of heart disease. During physical examinations, blood pressure, body height, body weight, and waist circumference were measured and heart physical examination was performed.

Laboratory investigation includes: routine blood analysis (hemoglobin, hematocrite, leukocyte, thrombocyte); CK, CKMB, troponin T, fasting and postprandial serum glucose level, glyco Hb, total cholesterol level, direct LDL cholesterol level, HDL and triglyceride cholesterol level, ureum, creatinine, SGOT, SGPT. Inflammatory response: serum IL-10 level.

Definitions

Acute coronary syndrome (ACS)[14,15] is defined as a spectrum of heart emergency consists of: acute myocardial infarction with ST elevation (ST-elevated myocardial infarction/ STEMI), acute myocardial infarction without ST elevation (non ST-elevated myocardial infarction / NSTEMI), unstable angina pectoris (UAP).

Unstable angina pectoris[16] is identified if fulfilling one of the following criteria: 1. Angina at rest and lasts for a long time, usually more than 20 minutes. 2. New onset angina classified as IIIrd class or above in the Canadian Cardiovascular Society (CCS) classification. 3. Acceleration of new angina with signs of increased severity of angina at least 1 CCS class to at least IIIrd class of CCS.

Acute myocardial infarction (AMI)[17] is diagnosed if there are characteristic elevation and gradual decline of troponin or early elevation and decline of biochemical markers of myocardial necrosis with at least one of the following symptoms: a. Ischemic symptoms, b. Occurrence of pathologic Q wave in the ECG. c. Changes in ECG waves indicating ischemia (elevation or depression of ST segment). d. Coronary artery intervention (e.g. coronary angioplasty).

Coronary artery disease (CAD) is a coronary heart disease in patients not currently having acute coronary syndrome.
based on anamnesis and ECG, proven history of CHD based on previous coronary angiography examination or having a history of acute myocardial infarction/ACS at least 6 months prior to the examination.

Body mass index (BMI) was measured in kg/m², and waist circumference was measured using SECA 200 measuring tape. Inflammatory Response was detected by measuring serum interleukin-10 level (in pg/mL) using enzyme immunoassay method (QuantikineR kit. R&D System, Inc., Minneapolis, MN, USA). Normal value is from not detectable (ND)–5.16 pg/mL. Intra assay variability was 6.6 –8.5% and inter assay variability was 8.1–15.6%.

**Blood sampling**

For routine blood analysis and blood chemistry analysis, peripheral venous blood was collected after a 10-12 hours fasting. Two hours later, the second blood sample was taken for postprandial blood glucose. Bloods were collected using standard method and sent to the Laboratory. Peripheral venous blood samples for serum IL-10 level measurement was collected using standard method and sent to the Laboratory.

**Data Processing and Analysis Technique**

All data obtained as continuous data. The data were then coded, tabulated, calculated and analysed using STATA. Normally distributed variables were analysed using parametric tests, and variables with abnormal distribution will be transformed into normal data range by logarithmic transformation, and then analysed with parametric test. The significant value of p < 0.05 is accepted as significant.

To compare the inflammatory response between ACS and CHD patient, the student-t test for independent samples was performed.

**RESULTS**

In the observational study from 1 May 2005 to 5 May 2006, as many as 62 CHD patients and 84 ACS that met the study criteria were enrolled. Demographic analysis showed that there was no difference in ages among the two groups.

The risk factors systolic and diastolic blood pressures, waist circumference and body mass index (BMI) did not differ significantly. Laboratory parameters such as fasting blood glucose and Glyco Hb level, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride level were not significantly different in the two groups.

Serum IL-10 level

The continuous data from IL-10 serum level was not normally distributed, we normalized the data using natural logarithm transformation as required for performing parametric statistical analysis. The serum IL-10 level is higher in ACS patients (Mean±SD) 7.37 ± 7.81 pg/mL; (95% CI: 5.68 - 9.07) compared with those in CHD patients (1.59 ± 1.55 pg/mL; 95% CI: 1.20 - 1.98).

To investigate whether IL-10 serum level could predict ACS, the sensitivity and specificity of this parameter towards SKA in various IL-10 serum levels were calculated. The optimal cut-off point with the highest sensitivity and specificity was IL-10 serum level > 1.95 pg/mL. The area under the receiver operating characteristic (ROC) curve for the sensitivity and specificity values for IL-10 serum level at various cut points was 0.88 as seen in Figure 1.
DISCUSSION

IL-10 serum level in ACS group

In this study, it was evident that the level of serum IL-10 in ACS patients was higher than that in CHD patients. The anti-inflammatory cytokine, IL-10 was abundantly released in the acute condition such as in ACS as a response to IL-6, compared with relatively stable CHD. This increase is supposedly aimed to maintain the balance of anti-inflammatory and pro-inflammatory factors in the body. This argument is supported by our finding that there was a strong, positive correlation between the level of serum IL-6 and IL-10 in CHD group (r=0.31; p=0.02).

In acute condition the body responds to maintain the balance between proinflammatory cytokine (IL-6) and antiinflammatory cytokine (IL-10), so any increase of IL-6 level in acute condition will be followed by an increase of IL-10.

In CAPTURE (c7E3 Antiplatelet Therapy in Unstable Refractory Angina) study, patients with increased IL-10 level have lower risk for death and for non-fatal myocardial infarction. Patients with increased both the hsCRP and IL-10 level showed lower risk compared to patients with increased hsCRP level alone without any increase in IL-10 serum level, suggesting that IL-10 might have a protective effect against the proinflammatory mediators in ACS.1

Studies on IL-10 level in other countries showed various results. A number of studies showed that in acute condition, there was a higher IL-10 serum level compared with that in stable condition. However, other studies reported lower IL-10 level in unstable angina pectoris.9,17 Smith et al.,9 firstly reported the lower IL-10 serum level in unstable angina pectoris compared with that in the stable angina pectoris. Målarstig et al.,12 reported that patients with ACS have higher IL-10 plasma concentrations than healthy controls. In contrast to previous studies, a high concentration of IL-10 on admission was associated with a crude risk increase of death and MI.
To predict the occurrence of ACS, the optimal cut-off point for serum IL-10 level is >1.95 pg/mL, with 79.76% sensitivity and 77.42% specificity. The sensitivity and specificity of various cut-off points for IL-10 level is also shown in Figure 1. Looking at the ROC curve, we are convinced that serum IL-10 measurement is a quite superior method to distinguish acute and stable condition, eventhough it is not as good as hsCRP for the same purpose.

It is concluded that the serum IL-10 level is higher in ACS patient group compared to CHD group.

REFERENCES