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Plasma histamine level as a distinguishing factor between stable coronary artery disease and acute coronary syndrome

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Abstract. Background: Angina can be caused by atherosclerosis in Coronary Artery Disease (CAD) patients either in Stable Coronary Artery Disease (SCAD) or Acute Coronary Syndrome (ACS). One of the mast cell-preformed mediator is histamine and it is suspected to be a part in atherosclerosis but the process is not fairly recognized, and there is lack of data in CAD population as well. To confirm the distinctness of plasma histamine level in patients with Acute Coronary Syndrome and Stable Coronary Artery Disease Patients. This was observational analytic study with transversal design in 49 CAD patients by purposive sampling, consist of 25 ACS patients (72% men, mean age 55,6±9,66 years) and 24 SCAD patients (83,3% men, mean age 52,71±8,03 years). The level of plasma histamine was measured using Histamine ELISA-Kit. Median values of plasma histamine level in ACS group and SCAD group were 30,79 ng/ml (5,85-36,09 ng/ml) and 26,42 ng/ml (0,30-41,39 ng/ml). Comparison analysis on median value of plasma histamine level between two groups was done with Mann-Whitney U Test and showed a statistically difference between two groups (p=0,011). There are significant differences in plasma histamine level between Acute Coronary Syndrome and Stable Coronary Artery Disease Patients.

1. Introduction

Coronary Artery Disease (CAD) is the leading cause of death in many countries. Although the mortality rate from CAD has declined over the past four decades, CAD remains responsible for 1 in 6 deaths in the United States in 2009 and around one-third or more of all deaths over the age of 35 years. [1, 2, 3] Riskesdas 2013 data shows that the prevalence of CAD in the population over the age of 15 in Indonesia was 1.5% [4].

CAD are divided into acute and chronic manifestations. Acute manifestations include an Acute Coronary Syndrome (ACS) consisting of Non-Elevation Acute Coronary Syndrome (NSTEACS) and ST-Elevation Myocardial Infarction (STEMI) while chronic manifestations are Stable Coronary Artery Disease (SCAD) Patients often present with chest pain or angina pectoris, which is a clinical manifestation of CAD that is often encountered in daily clinical practice. CAD patients are generally given medical therapy for anti-angina to treat their complaints. In some patients with CAD who have received anti-angina there are still complaints of angina pectoris. The mechanism of the occurrence of angina pectoris can be caused by various things that can disrupt the balance of myocardial oxygen demand and supply, which can occur during activity or at rest, and can be acute or chronic.

The process of developing a CAD is preceded by atherosclerosis in the coronary arteries. The atherosclerotic lesion can form a stenotic and non-stenotic lesions [7]. Stenosis that occurs in the coronary arteries is just a "tip of the iceberg" of a widespread and diffuse process of atherosclerosis. [8] The atherosclerosis begins with the formation of fatty streaks, an accumulation of foam cells and T cells in the tunica intima. The core of atheroma is surrounded by a layer of smooth muscle cells and collagen-rich matrix. At the peripheral of atheroma, there is a massive infiltration of T cells, macrophages, and mast cells. [9][10]

These mast cells are known to play a role in modulation of atherogenesis, so that the number of mast cells in the *shoulder region* of the atheroma has an enhanced effect risk of plaque rupture [9, 10, 11]. One of the mediators released by mast cells which has a role in the pathophysiology of SCAD and ACS, is histamine.

Histamine-related studies and their role in atherosclerosis have been widely carried out in vitro and in vivo in experimental animals, but histamine studies in CAD patients have not been widely performed. Based on an in vitro study, Lindstedt et al. reported that histamine causes dilatation of blood vessels so that it increases the permeability of blood vessels, resulting in local edema and withdrawal of inflammatory cells which then increases the risk of plaque erosion and rupture. The information about histamine in patients with CAD general and especially on patients with ACS and SCAD is still not widely available. Hence, this study will examine the differences in plasma histamine levels in both groups of the patients.

2. Methods

This is analytic observational study using a transversal study approach. The purpose of this study is to distinguish between plasma histamine level in patients with Acute Coronary Syndrome and Stable Coronary Artery Disease Patients, and analyze the correlation between plasma histamine levels and angina degrees based on the classification of the Canadian Cardiovascular Society (CCS).

This study was conducted at Emergency Room and Outpatient Clinic of Dr. Soetomo General Hospital Surabaya; ER's Clinical Pathology Laboratory and Diagnostic Center Building of Dr. Soetomo General Hospital Surabaya; and Laboratory of Hospital for Tropical Disease Universitas Airlangga Surabaya. The study was held at July 2015 to October 2015. The sample of this study was patients with coronary heart disease (CAD) in Surabaya during the study period. The study sample was CAD patients divided into Acute Coronary Syndrome (ACS) and Stable Coronary Artery Disease (SCAD) patients.

These are inclusion and exclusion criteria for this research.

Inclusion criteria:

- Age ≥ 20 years
- Willing to participate in research and sign an informed consent sheet
- SCAD patients, who are diagnosed based on history, physical examination, electrocardiogram (ECG) and echocardiography data, exercise stress test (EST) or previous coronary angiography
- ACS patients diagnosis based on history, physical examination, acute ECG changes and laboratory tests for cardiac marker levels (CKMB and troponin I)

Exclusion criteria:

- Have autoimmune disease
- Suffering from malignancy
- Taking anti-histamine drugs in 3 days before blood sampling
- History of taking long term corticosteroid drugs (more than 2 weeks) or short term corticosteroid (1 week) before blood sampling

Drop out criteria:

- Lysis blood samples and lipemic blood samples

The research sample was taken by purposive sampling, i.e. samples were taken from accessible populations with specific considerations until the minimum number of samples was met.

2.1. Research tools and material

Tools: syringes, vacuum blood tubes (Vacuette TM), eppendorf tube, rack tube, the cooler device for the storage of blood samples, cooling bag, centrifugation machine, plasma histamine counter machine by the method of Enzyme Linked Immunosorbent Assays (ELISA), ECG machine, sphygmomanometer, stethoscope, stature meter and weight scales .

Ingredients: 3 cc venous blood sample and Histamine ELISA Kit ABIN2115229

2.2. Research steps

ACS patients who came to emergency room of Dr. Soetomo General Hospital and SCAD patients who came to the outpatient, were conducted an early screening according to the inclusion and exclusion criteria.

After being explained about the procedure and sign an informed consent, patients with ACS and SCAD that meet the inclusion and exclusion criteria were performed anamnesis, physical examination, and the comprehensive examinations such as ECG and X-ray was checked from the past medical records. After that, 3 cc of venous blood was drawn. Patients in the SCAD group, blood sampling was carried out to the Clinical Pathology Laboratory at the Integrated Diagnostic Center Building (GPDT) Dr. Soetomo Hospital Surabaya. In patients with ACS group, blood sampling was performed during 24 hours since arriving at the Dr. Soetomo General Hospital, during the blood sampling process is always accompanied by a doctor to improve safety for patient safety.

Blood collected in vacuum blood tubes are labelled with the serial number of the sample. The blood was centrifuged immediately after collection and then plasma is taken and put in an eppendorf tube, placed in a tube rack and then stored inside a cooler with a temperature of -2.0°C. Then the sample was taken by using cool bag with dry ice to Laboratory of Hospital for Tropical Disease Universitas Airlangga for examination of histamine levels in plasma by using histamine ELISA - Kit ABIN2115229 according to the protocol in the kit.

After the data is collected, data analysis is performed.

2.3. Data processing and analysis

The data collection has gone through the process of coding, entering, cleaning, and editing. A descriptive statistical analysis was done on the basic characteristics of the research subjects including age, sex, angina degree based on the Canadian Cardiovascular Society, ECG interpretation, Body Mass Index (BMI), SCAD history, ACS history, history of diabetes mellitus, history of hypertension, history of dyslipidemia, smoking history, history of allergies, history of previous PCI procedures, Glomerular Filtration Rate (GFR) and lipid profile as well as plasma histamine levels. To find out whether the data obtained is normally distributed, a normality test is carried out. Inferential statistical analysis was conducted to test the hypothesis of differences in plasma histamine levels between groups of ACS patients and patients with SCAD by using Independent Student t-test (if the data is normally distributed). Mann Whitney-U test used if the data is not normally distributed. The relationship between plasma histamine levels with the degree of angina based on the classification of the Canadian Cardiovascular Society was analysed using the Spearman Rank Correlation Test. Different analysis between variables in the ACS and SCAD groups with categorical data types were performed by Chi-square (X 2) test or with Fisher's Exact Test if the cell values were small. Categorical scale data l displayed in the form of frequency distributions and percentages, while numerical scale data will be displayed in the form of a mean ± standard intersection or median and range of values. A $p < 0.05$ indicates statistical significance [14].

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 20.0.

3. Results

25 patients with ACS and 24 patients with SCAD who met the inclusion and exclusion criteria were included in this study. This number meets the minimum sample determined by the *sample size formula* that is equal to 20 research subjects for each group.

3.1. Basic characteristics of research subjects.

ACS patients consisted of 18 male subjects (72%) and 7 female subjects (28%) while in the SCAD patients group consisted of 20 male subjects (83.3%) and 4 female subjects (16, 7%). The average age of the subjects in the ACS group was 55.6 ± 9.66 years, while the SCAD group was 52.71 ± 8.03 years. In the ACS group there were 1 person who had a history of SCAD (4%), 1 person with previous ACS history of (4%), 13 persons with diabetes mellitus (52%), 17 persons with hypertension (68%), 15 persons with smoking history (60%), 5 persons with history of dyslipidemia (20%), 1 person with history of Chronic Kidney Disease (CKD) (4%), and no one has a history of allergies or history of undergo Percutaneous Coronary Intervention (PCI) before.

In the group of SCAD there were 24 persons with history of SCAD (100%), 13 persons with history of ACS (54 , 2 %), 11 persons with diabetes mellitus (45.8 %), 17 persons with hypertension (70, 8%), 18 persons with smoking history (75 %), 17 persons with history of dyslipidemia (70.8 %), 2 persons with history of CKD (8.3 %), 3 persons with history of allergy (12.5%) and 13 persons with history of having undergone previous PCI procedures (54.2%). Some other examination parameters including angina degree, Body Mass Index (BMI), Glomerular Filtration Rate (GFR) based on Cockroft-Gault, blood fat profile levels (total cholesterol, LDL, HDL, triglyceride, and ratio of total cholesterol to HDL) and an electrocardiogram. A summary of the basic characteristics of the research subjects from the two groups can be seen in table 3.1.

Table 1. Basic characteristics of the study subjects (n = 49).

Variable	*ACS* group (n = 25)	*SCAD* group (n = 24)	*P*
Gender			
Male (%)	18 (72%)	20 (83.3%)	0, 496 [d]
Female (%)	7 (28%)	4 (16.7%)	0.496 [d]
Age (years)	55.6 ± 9.66	52.71 ± 8.03	0,400 [c]
BMI (kg/m^2)	25.2 ± 2.78	25.07 ± 4.93	0.271 [c]
SCAD history (%)	1 (4%)	13 (54.2%)	<0.001 [c]
Degree of angina			
CCS I	0 (0%)	5 (20.8%)	<0.001 [c]
CCS II	0 (0%)	17 (70.8%)	<0.001 [c]
CCS III	9 (36%)	2 (8.3%)	<0.001 [c]
CCS IV	16 (64%)	0 (0%)	<0.001 [c]
ACS history (%)	1 (4%)	13 (54.2%)	<0.001 [d]
Diabetes mellitus (%)	13 (52%)	11 (45.8%)	0.666 [c]
Hypertension (%)	17 (68%)	17 (70.8%)	1,000 [d]
Dyslipidemia (%)	5 (20%)	17 (70.8%)	<0.001 [c]
Smoking history (%)	15 (60%)	18 (75%)	0.364 [d]
CKD history (%)	1 (4%)	2 (8.3%)	0.609 [d]
Allergy history (%)	0 (0%)	3 (12.5%)	0,110 [d]
Previous *PCI* history (%)	0 (0%)	13 (54.2%)	<0.001 [d]
GFR (ml / minute)	69.37 ± 27.26	77.44 ± 32.88	0.354 [a]
Total cholesterol (mg/dl)	176.76 ± 26.75	184.54 ± 39.6	0,427 [a]
LDL (mg / dl)	119.64 ± 24.21	123.13 ± 51.27	0.749 [b]

HDL (mg / dl)	29.12 ± 6.9	33.17 ± 9.39	0.042 [b]
Triglycerides (mg/dl)	167.56 ± 69.56	171.5 ± 88.77	0.889 [b]
TC/HDL ratio	6.38 ± 1.8	6.07 ± 2.67	0.267 [b]
ECG picture			
Elevation ST segment (%)	20 (80%)	0 (0%)	<0.001 [c]
ST depression or T inversion (%)	4 (16%)	4 (13.3 %)	<0.001 [c]
Pathological Q (%)	0 (0%)	14 (46.7 %)	<0.001 [c]
Normal (%)	0 (0%)	5 (16.7 %)	<0.001 [c]
Others (%)	1 (4%)	1 (3.3 %)	<0.001 [c]

Information:
Numerical scale data will be displayed in the mean ± standard intersection and analyzed by the *Independent S tent Test* (*=a) if the distribution is normal, or by *Mann-Whitney U Test* (†=b) if the distribution is not normal. Data categorical scale is displayed in the form of a frequency distribution and percentage (%) and [c] analyzed with X^2 *test* (‡=c) or if the value of small cells with *Fisher's Exact Test* (§=d) .

3.2. Plasma histamine levels in group ACS

Plasma histamine levels in the ACS group are shown in table 2. In the ACS group, the median value of plasma histamine levels was 30.79 ng/ml with a value range of 5.86 - 36.09 ng/ml.

Table 2. Plasma histamine levels in *ACS* group (n = 25).

Variable	Median	Minimum	Maximum
Plasma Histamine Levels (ng/ml)	30.79	5.86	36.09

3.3. Plasma histamine levels in the SCAD group

Plasma histamine level data in SCAD groups are shown in table 3. In SCAD group, the median value of plasma histamine levels was 26.42 ng/ml with a range of values ranging from 0, 30 - 41.39 ng/ml.

Table 3. Plasma histamine levels in *SCAD* group (n=24).

Variable	Median	Minimum	Maximum
Plasma Histamine Levels (ng/ml)	26,42	0,30	41,39

3.4. Differences in plasma histamine levels between two groups

Analysis of differential in plasma histamine levels between ACS and SCAD patients are shown in table 4. The normality test was conducted using the Kolmogorov-Smirnov test and the result distribution of histamine data is not normal ($p < 0.05$), so that inferential analysis is performed using the Mann-Whitney U Test and histamine levels shown in the median between the range of minimum and maximum value. The results of the Mann-Whitney U Test showed significant differences from plasma histamine levels between ACS and SCAD patients with median values of plasma histamine levels in ACS and SCAD patients was 30.79 ng/mL and 26.42 ng/ml, respectively, wherein both the median difference was statistically significant, $p = 0.011$ ($p < 0.05$).

Table 4. Analysis of differences in plasma histamine levels between the two groups.

Variable	*ACS* Group (n=25)		*SCAD* Group (n=24)		$p^{\dagger}$
	Median	Min-Max	Median	Min-Max	
Plasma Histamine Levels (ng/ml)	30,79	5,86-36,09	26,42	0,30-41,39	0,011[a]

a: Analyzed with Mann-Whitney U Test

3.5. Plasma histamine levels based on the angina classification

Data of plasma histamine levels based on the classification of angina according to the Canadian Cardiovascular Society on the whole subject of the study are shown in table 5.

Table 5. Plasma histamine levels based on classification of angina degrees.

Degree of angina (n=49)	Plasma Histamine Level (ng/ml)		
	Median	Minimum	Maximum
CCS I	26,27	3,2	31,18
CCS II	26,44	0,3	41,39
CCS III	30,62	12,83	34,19
CCS IV	32,08	5,86	36,09

3.6. Interrelationship between plasma histamine level and degree of angina

Correlation analysis between plasma histamine levels and angina levels based on the Canadian Cardiovascular Society is shown in table 6. This inferential analysis is done using the Spearman Rank Correlation Test and the correlation was moderately positive [15] and statistically significant r (49) = +0,379, p = 0.007, two-tailed between plasma histamine levels with angina degrees. In this case, when plasma histamine levels was increases, the degree of angina was also increases.

Table 6. Correlation analysis between plasma histamine levels and angina degrees.

Variable	*p*	*r*
Plasma Histamine Levels and Degrees of Angina	0,007†	0,379

† Analyzed using the Spearman Rank Correlation Test

4. Discussion

This study shows the characteristics of most patients with CAD, in both groups, ACS and SCAD were male with a mean age of 55.6 ± 9.66 and 52.71 ± 8.03 years, respectively. Traditional risk factors such as diabetes mellitus, hypertension, obesity and smoking were found in both groups but there were significant differences in the history of dyslipidemia in which the SCAD group had more subjects who have a history of dyslipidemia in 17 (70.8%). But in the examination of lipid profiles by examining the total cholesterol, LDL, HDL, and triglycerides, there were no significant differences in characteristics of lipid profiles between two groups. These findings was in line with existing epidemiological data [16]. Clinical manifestations of coronary artery atherosclerosis in the form of angina was measured by the degree classification of The Canadian Cardiovascular Society (CCS) in which the group SCAD patients is included in the category of CCS II (70.8%), while the group of ACS is CCS IV (64%). In CAD group, no subjects experienced angina with the CCS IV classification. More than half of the patients (54.2%) in CAD group had a history of previous SCAD or ACS and had undergone PCI procedures. In ACS group, no subjects experienced angina with the CCS I and CCS II classification.

The proportion of patients from group ACS with ST-elevation as ECG result is 20 persons (80%). While non ST elevation is 5 persons (16 %) respectively. This is different from proportion to Global Registry of Acute Coronary Events (GRACE) Study conducted in 14 countries where most of the presentations of ACS patients are NSTE-ACS which is as much as 62 % of 44,372 patients [17]. In *The Second Euro Heart Study on ACS* (EHS-ACS) conducted in 32 countries, the proportion of patients with STEMI and NSTE-ACS is almost the same amount, as much as 47% and 48% from 6385 patients [18]. This difference can be explained that the place where the research was carried out only in one hospital which is a tertiary referral hospital and NSTE-ACS cases can already be handled by other hospitals so that not all ACS cases are referred to the research site.

In this study, the median plasma histamine level in the ACS group was 30.79 ng/ml. In a previous study by Clejan et al. in the United States, the mean histamine blood levels in ACS patients were 84.5 ± 10.9 ng/ml which was much higher than the median values obtained in the ACS group in this study. 1 5 N The median value of the ACS plasma histamine group in this study was lower than the mean value

of the control patients in the Clejan et al. and Zdravkovic et al studies (30.79 ng/ml vs. 38.8 ± 8.7 ng / ml vs. 44.87 ± 1.09 ng/ml, respectively) [12,19]. Race population in this study is different from the previous study population where the difference in population can lead to differences in baseline plasma histamine levels whereas there are no data or previous studies on plasma histamine levels in Indonesia. In the study of Zdradkovic et al. reported histamine levels in the ACS group reached a peak in the examination 48 hours after the onset of chest pain so that in this study lower plasma histamine levels were also likely due to plasma histamine levels not yet reached its peak.[19] The range of plasma histamine levels in the ACS group was quite wide, i.e. between 5.86 - 36.09 ng / ml with blood sampling from all patients in this group carried out in less than 24 hours after the patient arrived at IRD. This conditions can be caused by the onset of different chest pain.

In the SCAD group, the median plasma histamine level was 26.42 ng/ml. In a previous study by Clejan et al. and Zdradkovic et al., higher histamine levels were obtained, namely 73.6 ± 11.1 ng/ml and 79.5 ± 3.6 ng/ml respectively [12,19]. In both previous research reports, there was no mention of PCI in the SCAD group while in this study more than half of the respondents had undergone PCI so apart from being a population difference, a history of having undergone PCI procedures was also a factor which plays a role, but this still needs to be further proven[12,19]. Range values of plasma histamine in the SCAD group of this study were extensive, i.e. between 0.30 - 41.39 ng/ml. The cause of this wide range of values is unknown because there is no basic data to compare with the same population.

In this study, the distribution of plasma histamine level data was abnormal, so the median values between both groups need to be compared each other. In both groups, there were no differences in age, sex, BMI, risk factors for diabetes mellitus, hypertension, smoking history and lipid profile. The results showed a statistically significant difference in plasma histamine levels between the ACS group and the SCAD group, 30,79 ng/ml (value range 5.86-36.09 ng/ml) and 26.42 ng/ml (value ranges from 0.30 to 41.39 ng/ml), p = 0.011. These results are consistent with the results obtained from previous studies by Clejan et al. where there were significant differences of histamine levels in the ACS, SCAD and control groups [12]. Zdradkovic et al. also obtained similar results in which the histamine levels in the group of ACS-STEMI was higher significantly compared with SCAD and when compared with the control group value is greater about two to three times [19]. The results of this study reinforce the results of previous studies that there are differences in levels of histamine in the spectrum of patients CAD. The lower value of overall histamine levels compared to previous studies can be caused by different populations study so that the possibility of basic histamine levels in each population is different.

Subanalysis was conducted to determine the correlation of plasma histamine levels with angina degrees based on the classification of the Canadian Cardiovascular Society [6,20]. Highest median values was obtained in the subjects with the degree of angina CCS IV, while the lowest median value was obtained on the subjects with the degree of angina CCS I. There were no other studies that correlate plasma histamine levels with angina degrees. However, from the statistical test results using the Spearman Rank Correlation Test between plasma histamine levels and angina degrees, a moderately positive correlation was found, which was statistically significant. This result shows that when plasma histamine levels increase, the degree of angina also increases. In the study of Wang et al. in mice that were genetically designed to be histamine deficiencies and compared to controls, there was less atherosclerosis in mice with histamine deficiency [21]. The results of this study reinforce the results of previous studies, where histamine can cause vasodilation and increased the permeability of capillary arteries in atherosclerotic plaques so that bleeding occurs in the plaque and consequently when the intima thickens and the lumen of the coronary arteries becomes narrower, it can also cause coronary artery spasm [13,14]. Narrowing due to atherosclerotic plaques and coronary artery spasm can also cause angina. The histamine release in the atherosclerotic plaque will cause progression of atherosclerotic plaque, accelerate the occurrence of plaque rupture and thrombosis, which can result in occlusion of the coronary arteries [12]. As a result of the plaque rupture, histamine can be released into the circulatory system [22].

This study has weaknesses such as the absence of a control group, and there was no preliminary study that should conducted to determine the basic value of histamine. Examination of blood samples in a

laboratory with a different place from the place of blood sampling also has a potential effect in the results of histamine levels data. Because, despite various efforts to maintain the temperature both by using cool boxes and dry ice, there is still possibility of sample damage caused by the process of thawing during the trip.

5. Conclusion

The differential in plasma histamine levels between patients with Acute Coronary Syndrome and Stable Coronary Artery Disease was statistically significant. There was also a moderate positive correlation between plasma histamine levels and angina degrees that were statistically significant.

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