Clinical research

Correlation between leukocyte count and infarct size in ST segment elevation myocardial infarction

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Abstract

Introduction: Regarding the inflammatory mechanisms involved in ischemic heart disease, currently the leukocyte count is the subject of studies related to its association with the prognosis and mortality of ST segment elevation myocardial infarction (STEMI). Our aim is correlate the leukocyte count rise with the size of STEMI, evaluated with the area under the curve (AUC) and the peak of necrosis markers release.
Material and methods: This study is a sub-analysis of the TETHYS trial, a clinical trial that evaluated the effects of methotrexate in STEMI. We evaluated the correlation between quantitative variables with Pearson's correlation, and the variables that did not follow a normal distribution were subjected to logarithmic transformation to base 10. The value of $p < 0.05$ indicated statistical significance.
Results: Males accounted for 73% of the participants, who had an average age of 59 years. A total of 58% were hypertensive and 53% smokers. The leukocyte count at hospital admission was significantly correlated with the AUC creatine kinase (CK) ($r = 0.256$, $p = 0.021$), troponin AUC ($r = 0.247$, $p = 0.026$), peak CK ($r = 0.270$, $p = 0.015$) and troponin peak ($r = 0.233$, $p = 0.037$). The leukocyte count at 72 h was significantly correlated with CK AUC ($r = 0.238$, $p = 0.032$), AUC of MB portion of CK ($r = 0.240$, $p = 0.031$) and peak CK ($r = 0.224$, $p = 0.045$).
Conclusions: White blood cell count correlates with STEMI size assessed by serial cardiac biomarker levels.

Key words: myocardial infarction, leukocyte count, leukocyte.

Introduction

Ischemic diseases cause one of every six deaths. Every 34 s an American experiences a coronary event, and every minute, another dies due to the same factor [1]. Acute myocardial infarction is one of the consequences of ischemic diseases and has in its pathophysiological process a clear inflammatory involvement: there is an increase of nuclear factor κB (NF-κB) and the levels of proinflammatory cytokines, and there is adherence of polymorphonuclear leucocytes [2]. There is also an increase in the number of leukocytes after the onset of symptoms of ischemic disease, and it is much larger when there are significant injuries [3]. These factors have stimulated the search for potential anti-inflammato-

ry therapeutic targets for cardiovascular disease [4–12].

Based on the existence of this mechanism, currently, the blood leukocyte count is the subject of studies, not only in order to characterize it as an inflammatory marker, a fact that is proven, but also as a way to prove its relationship with cardiac events [13], increased mortality [14–16] and severity of myocardial infarction [17, 18]. In addition, it has been shown, too, that an increased white blood cell count signals a period of increased risk for recurrent ischemic events, where this increase precedes the risk by a week, and is associated with increased in-hospital mortality [19–21].

Although studies have already related the WBC count to the severity of myocardial infarction [17, 18] and increased mortality [14–16, 20], no one has correlated directly leukocyte count with the size of acute myocardial infarction with STEMI. Given this gap in the knowledge, this study presents the hypothesis that there is a correlation between leukocyte count and the STEMI size estimated by the area under the curve of myocardial necrosis markers. This correlation could represent an important new risk stratification and prognostic tool for patients who suffer STEMI.

Material and methods

It is a cross-sectional study constituting a subanalysis of the study Methotrexate Therapy in ST Segment Elevation Myocardial Infarctions: a randomized double-blind, placebo-controlled trial (TETHYS trial), whose design has been described previously [13]. An evaluation of the data of 81 patients with a diagnosis of confirmed STEMI who were included in the study from April 2013 to June 2014 was performed.

Following the criteria of the TETHYS study, included patients had to be older than 18 years, with chest pain suggestive of acute myocardial infarction that started within 12 h, electrocardiogram showing elevation of the ST segment ≥ 2 mV at a minimum of two consecutive times, and primary angioplasty. Excluded were patients with previous myocardial infarction, heart failure history, angioplasty in the last 3 months, heart failure or cardiogenic shock, previous renal failure (serum creatinine > 2 g/dl), alcohol consumption (≥ 20 drinks per week), illegal drug use, rheumatoid arthritis, cancer, infectious diseases, prior anemia (hematocrit below 30%), use of steroidal anti-inflammatory or nonsteroidal drugs in the last week, excessive consumption of xanthine (more than two and a half glasses of coffee or two and a half gourds of mate and pregnancy.

The primary endpoint in this study was the correlation of leukocyte count (on admission and 72 h) with infarct size measured by the area under the curve (AUC) of creatine kinase (CK). Secondary outcomes included the correlation of WBC count with the AUC of MB portion of CK (CK-MB) mass and troponin I, the white blood cell count with CK, CK-MB mass and troponin peaks and the white blood cell count with left ventricular ejection fraction (LVEF). The infarct size measured by AUC of CK, CK-MB and troponin I was calculated by the linear-trapezoidal method from the serum measurements taken every 6 h for 72 h. If the baseline or 72 h measurements were unavailable, the corresponding value was set to 0. For missing values at intermediate times, linear interpolation was used. The infarct size was also evaluated by CK peaks, CK-MB and troponin I. The WBC count was assessed on admission and at 72 h. All samples were analyzed in the local laboratory. Left ventricular ejection fraction was assessed by transthoracic echocardiography (Vivid E9 system, General Electrics) at 72 h and after 3 months. Mortality was assessed at 3 months.

Statistical analysis

Data were analyzed with SPSS 13.0 software. Continuous variables were presented as the mean and standard deviation or median and interquartile range when they did not follow a normal distribution, whereas qualitative variables were presented as the absolute number and percentage. Fisher's exact test was used to evaluate categorical variables, whereas Student's *t* test for independent samples was used to evaluate continuous variables. The correlation between quantitative variables was assessed by Pearson's correlation, and variables that did not follow a normal distribution were subjected to logarithmic transformation to base 10 for further evaluation with Pearson's correlation. The value of $p < 0.05$ indicated statistical significance. The study was approved by the local ethics committee.

Results

We evaluated 81 patients who were enrolled in the study from April 2013 to June 2014. The sample consisted of 59 (72%) men. The remaining basic characteristics of the population, mean leukocyte count as well as the median AUC and peak cardiac biomarkers are presented in Table I.

The correlation between WBC count with areas under the curve and peaks of cardiac biomarkers is presented in Table II. The correlation between logarithmic transformation of AUC CK with admission leukocyte count and leukocyte count at 72 h showed a significant but weak positive correlation ($r = 0.256$, $p = 0.021$ and $r = 0.238$, $p = 0.032$, respectively). Similarly, there is a correlation between admission leukocyte count and logarithmic trans-

Table I. Characteristics of patients at baseline

Variables	Values
Age [years]*	59 ±11.4
Men, *n* (%)	59 (73)
Risk factors, *n* (%):	
Hypertension	47 (58)
Dyslipidemia	27 (33)
Smoking	43 (53)
Family history of coronary disease	24 (29)
Anterior wall involvement, *n* (%)	32 (39)
Infarct size – median (IQR):	
AUC CK	74448 (43276.5–103338)
AUC CK-MB	9423.3 (3808.2–12387.1)
AUC troponin	3193.5 (1278.9–5675.9)
CK peak	2446 (1305.5–3665.5)
CK-MB peak	469.8 (204.2–646.5)
Troponin I peak	106.3 (41.2–223.5)
Admission leukocyte count*	13294 ±4632
Leukocyte count at 72 h*	9320 ±3048.5

**Values expressed as mean ± standard deviation; IQR – interquartile range, AUC – area under the curve, CK – creatine kinase, CK-MB – MB portion of CK.*

Table II. Correlation between infarct size and leukocyte count*

Infarct size	Admission leukocyte count		Leukocyte count at 72 h	
	r	*p*	*r*	*p*
Log AUC CK	0.256	0.021	0.238	0.032
Log AUC CK-MB	0.207	0.064	0.240	0.031
Log AUC troponin	0.247	0.026	0.198	0.077
Log peak CK	0.270	0.015	0.224	0.045
Log peak CK-MB	0.185	0.097	0.195	0.081
Log peak troponin	0.233	0.037	0.174	0.120

**Logarithmic transformation to base 10; AUC – area under the curve, CK – creatine kinase, CK-MB – MB portion of CK.*

formation of AUC troponin, and peaks of CK and troponin. There is a correlation between leukocyte count at 72 h and logarithmic transformation of AUC CK-MB and CK peak (Table II).

In the period of 3 months after the STEMI event, 6 of 81 patients died (7%). The average white blood cell count on admission was not associated with mortality: for the average patient who died at 3 months it was 13976.6 ±6058.6/μl, while for the other patients it was 13239.4 ±4546.9/μl (p = 0.710). Likewise, at 72 h the mean leukocyte count of patients who died within 3 months was 12181.6 ±5476.5/μl, and for other patients it was 9092 ±2702.5/μl (p = 0.227).

There was no significant correlation between WBC count on admission and ventricular function assessed by ejection fraction of the left ventricle: LVEF at 72 h showed r = –0.053, p = 0.640 and LVEF at 3 months r = –0.093, p = 0.420. The leukocyte count at 72 h did not show a significant correlation with LVEF: LVEF at 72 h showed r = –0.066, p = 0.560 and LVEF at 3 months r = –0.015, p = 0.890.

Discussion

Our study has important findings relating leukocyte count and STEMI size measured by cardiac biomarkers.

Despite the fact that the study in question did not use imaging tests such as myocardial magnetic resonance imaging (MRI), assessment of infarct size by AUC of myocardial necrosis markers release is widely known and used, even as an endpoint in randomized controlled trials [4, 7]. With some exceptions, the logarithmic transformation of AUC of biomarkers and the peaks of these markers show positive correlations with the leukocyte count at admission and at 72 h. Case-control studies in previously healthy patients have shown an association between WBC count and coronary heart disease: a leukocyte count greater than 8000 apparently has a stronger association with coronary heart disease [22, 23]. Other studies have shown that white blood cell count of patients with myocardial infarction is independently associated with mortality and in-hospital medical complications, as well as a higher incidence of congestive heart failure and death [24, 25].

The reason for the association of WBC count with unfavorable outcomes and poor prognosis in myocardial infarction is based primarily on inflammation caused by a coronary event. The mechanisms of the increase in inflammatory cells and active secondary leukocytes range from biochemical, biomechanical and hematological to electrical. It was reported that leukocytes are able to cause oxidative and proteolytic injury of the coronary arteries, being able to aggregate, impacting the microvasculature, and causing hypercoagulable and electrical instability in the heart [26]. All these mechanisms lead to lower coronary perfusion and therefore increased size and severity of the event.

Despite the correlation between infarct size and leukocyte count, there was no significant

correlation between leukocyte and ventricular function assessed by echocardiography. These findings were unexpected, and contrast with the results showing correlations between logarithmic transformation of AUC and biomarker peaks. Furthermore, the findings differ from the literature, which indicates a negative correlation between the leukocyte count and the function of the left ventricle [27].

This study has some limitations that should be mentioned: despite adequate power to assess substitute outcomes, there was a lack of power to demonstrate the association between mortality at 3 months and WBC count. New studies with long-term follow-up as well with a larger sample may demonstrate that such a relationship might have a greater impact, agreeing then with the literature. The limitations, however, do not invalidate the data; from the results obtained in this study one can use the patient's white blood cell count with STEMI as another prognostic tool, allowing stratification even if it is more detailed and specific, allowing then a more targeted and individualized treatment.

In conclusion, the WBC count of admission relates to the STEMI size assessed by AUC CK, AUC troponin, CK peak and troponin peak. Already the WBC count at 72 h correlates with the size of STEMI as measured by AUC CK, AUC CK-MB and CK peak. The white blood cell count has no association with mortality or left ventricular function in this study.

Conflict of interest

The authors declare no conflict of interest.

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