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PROGNOSTIC VALUE OF P-SELECTIN IN PATIENTS WITH STABLE ANGINA PECTORIS

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Coronary artery disease for many years is being the main cause of death in many developed countries. Currently, cardiovascular disease (CVD) plays the main role in the evolution of the total mortality in the world. Most deaths occur as a result of coronary heart disease (more than 300 thousand per year). It is known that chronic inflammation is a marker of global endothelial dysfunction and may be associated with the increased risk of cardiovascular events in patients with coronary artery disease. Nowadays, it is very promising in terms of assessing the prognosis and course of the disease to study P-selectin.

KEY WORDS: angina pectoris, P-selectin, clopidogrel, inflammation

ПРОГНОСТИЧНЕ ЗНАЧЕННЯ РІВНЯ Р-СЕЛЕКТИН У ХВОРИХ НА СТАБІЛЬНУ СТЕНОКАРДІЮ

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ІХС протягом багатьох років є головною причиною смертності населення в багатьох економічно розвинених країнах. В даний час серцево-судинні захворювання (ССЗ) відіграють вирішальну роль в еволюції загальної смертності у світі. Найбільше смертей настає внаслідок ішемічної хвороби серця - понад 300 тис. випадків на рік. Відомо, що хронічне запалення є маркером розвитку глобальної ендотеліальної дисфункції і може бути пов'язане з підвищеним ризиком розвитку серцево-судинних ускладнень у хворих на ішемічну хворобу серця. На сьогоднішній день, дуже перспективним щодо оцінки прогнозу і перебігу захворювання є Р-селектін.

КЛЮЧОВІ СЛОВА: стабільна стенокардія, Р-селектин, клопідогрель, хронічне запалення

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ УРОВНЯ Р-СЕЛЕКТИНА У БОЛЬНЫХ СТАБИЛЬНОЙ СТЕНОКАРДИЕЙ

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ИБС в течение многих лет является главной причиной смертности населения во многих экономически развитых странах. В настоящее время сердечно-сосудистые заболевания (ССЗ) играют решающую роль в эволюции общей смертности в мире. Больше всего смертей наступает вследствие ишемической болезни сердца – более 300 тыс. случаев в год. Известно, что хроническое воспаление является маркером развития глобальной эндотелиальной дисфункции и может быть связано с повышенным риском развития сердечно-сосудистых осложнений у больных с ИБС. На сегодняшний день, очень перспективным в отношении оценки прогноза течения заболевания является Р-селектин.

КЛЮЧЕВЫЕ СЛОВА: стабильная стенокардия, Р-селектин, клопидогрель, хроническое воспаление

INTRODUCTION

Despite the optimal therapy, which has significantly reduced the cardiovascular mortality in industrialized countries, it remains at a sufficiently high level [1]. One of the most promising directions for further reducing the «residual» cardiovascular risk is the reduction of systemic inflammation [2]. To date, high-sensitivity C-reactive protein is used as a standard for assessing the level of systemic inflammation, which is not inferior

in terms of prognostic significance for adverse outcomes to LDL cholesterol [3], however, various mechanisms that take place through the systemic inflammatory response different cell types that produce cytokines, chemokines, adhesion molecules, which may not have the same degree of activation in patients [4]. One of the ways of individualizing therapy for patients with high cardiovascular risk is the evaluation of new biomarkers, including P-selectin, reflecting at the individual level different ways of activating the systemic inflammatory response. Based on this, a study of the prognostic value of the P-selectin level for large adverse events in patients with stable angina may provide new opportunities in reducing the «residual» cardiovascular risk.

OBJECTIVE

The aim of the study is to study the prognostic value of the P-selectin level for adverse outcomes in patients with stable angina.

MATERIALS AND METHODS

The study included 89 patients, 27 of them women and 62 men aged 38 to 89 years (mean age 63.2 ± 11.8 years), who had stable angina on the basis of clinical manifestations, these stress tests and coronaroangiography in accordance with the recommendations of the European Society of Cardiology 2013 [5].

Patients included in the study were tested in addition to standard methods to determine the level of a new biomarker of P-selectin inflammation and a reference marker of systemic inflammation, high-sensitivity CRP (hs-CRP). For the quantitative determination of P-selectin, a set of reagents «Human sP-selectin Platinum ELISA» was used. The minimum detectable concentration of P-selectin was 0.2 ng/ml. For the quantitative determination of hs-CRP, a set of reagents «SRB-IFA-Best (highly sensitive)» was used. The determined concentration of CRP was 0.1-10 mg/l. Specificity of the assay was provided by the use of monoclonal antibodies, which are highly specific for CRP.

All patients underwent standard therapy in accordance with these recommendations, except in cases of contraindications and intolerance of the drugs. The presence of adverse cardiovascular events was assessed prospectively in 3 years from the inclusion of patients in the study at the total end point (cardiovascular death, nonfatal myocardial infarction, unstable angina, ischemic cerebral stroke, transient ischemic attack, revascularization). To compare the differences between groups with different initial levels of P-selectin, the Kaplan-Meier procedure was used to construct the cumulative survival curves.

RESULTS AND DISCUSSION

In general, in the group of patients with verified stable angina, the average P-selectin level in plasma was 90.0 + 46.5 ng/ml and hs-CRP 6.2 + 4.2 mg/l. In the correlation analysis, no correlation was found between the plasma levels of P-selectin and hs-CRP in the examined patients ($r = -0.131$, $p = 0.284$). A weak negative correlation between the indices did not reach certainty.

After three years, myocardial infarction with ST segment elevation in 3 patients, acute coronary syndrome (unstable angina) was recorded in 9 patients, 2 patients underwent revascularization of coronary vessels, ischemic stroke in 3 patients was diagnosed and 2 patients died due to cardiovascular diseases.

The analysis was performed on the total primary endpoint in patients, depending on the initial level of P-selectin. Patients were divided into groups depending on the initial level of P-selectin: more and less median and on tertili.

When comparing 2 groups of patients with P-selectin level, more and less median revealed a tendency (Fig. 1), which did not reach the significance, to a greater number of cardiovascular events in patients with P-selectin level above the median.

In the cumulative analysis of events in patients divided into groups according to the trotyl, depending on the initial level of P-selectin (Fig. 2), it was found that the number of events in group 1 patients (lower tertile in P-selectin level) was significantly lower than in patients patients of group 3 (upper tertile by the initial level of P-selectin).

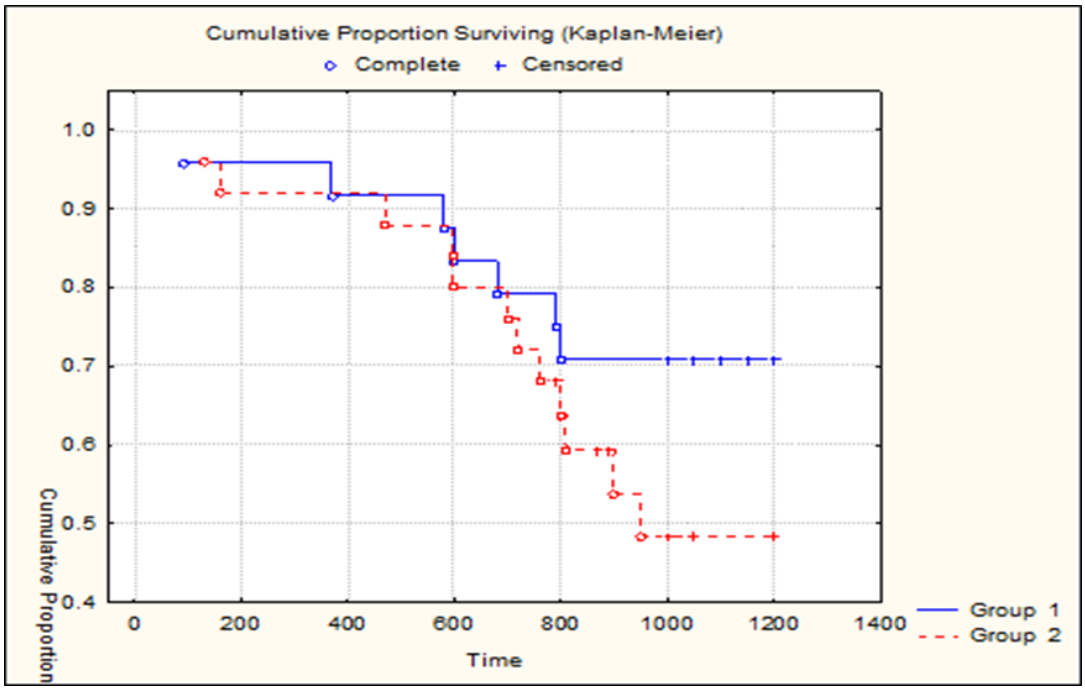

Fig. 1. Comparison of the cumulative number of events in patient groups, depending on the initial level of P-selectin (Kaplan-Meier procedure). Group 1 – patients with a P-selectin level below the median, group 2 – patients with a P-selectin level above the median (significance of differences between groups p = 0.29).

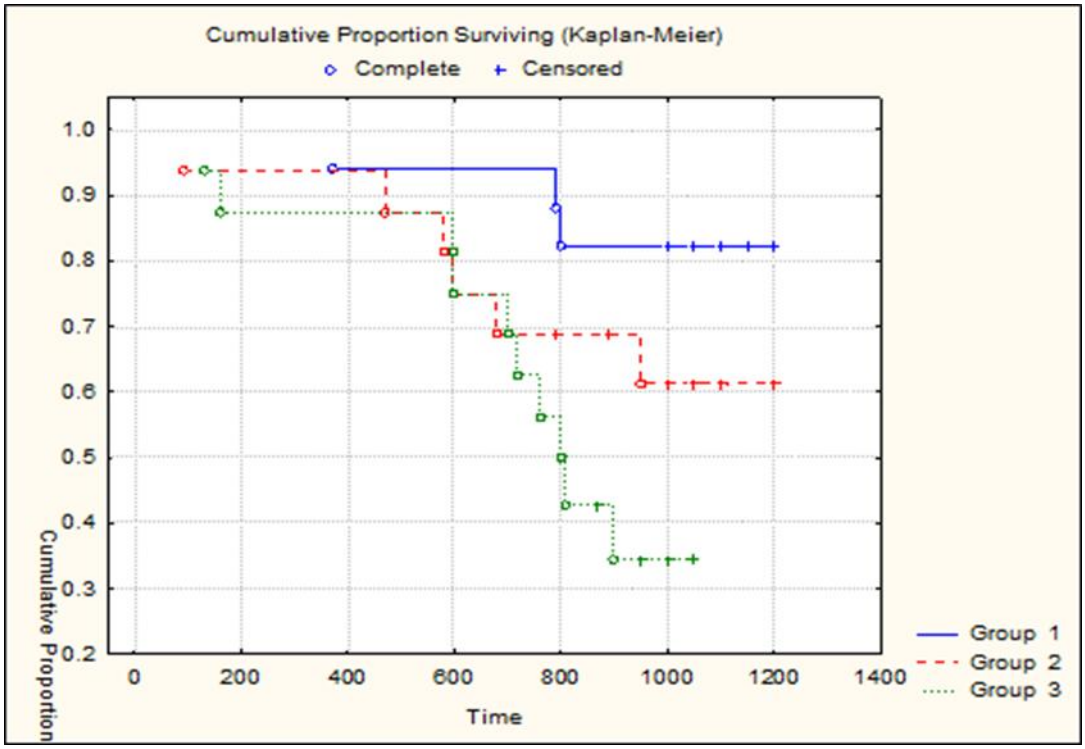

Fig. 2. Comparison of the cummulative number of events in patient groups, depending on the initial level of P-selectin (Kaplan-Meier procedure). Group 1 – patients with P-selectin level in the lower tertile, group 2 – patients with patients with P-selectin level in the middle tertile, group 3 – patients with P-selectin level in the upper tertile (significance of differences between groups 1 and 3 – p = 0.046).

Thus, a significantly greater number of cardiovascular events in patients with a high baseline P-selectin level (upper tertile) were found compared with a lower level (lower tertile). Given the lack of correlation between the level of P-selectin and the standard biomarkerhs-CRP, this creates the perspective not only for obtaining additional prognostic information in patients with angina with the help of P-selectin level estimation, but also for use in the therapy of specific inhibitors of various cytokines, chemokines, molecules adhesion, etc., which is confirmed by randomized studies using inclucumab [6] and kanakinumab [7].

However, experimental data should be taken into account that the soluble P-selectin studied in our study is only a marker of the platelet component of the inflammatory response, and its dimeric form is the active mediator [8].

CONCLUSIONS

1. The level of P-selectin in patients with stable angina is not associated with the level of hs-CRP, which creates the prerequisites for the personalization of therapeutic goals for reducing the systemic inflammatory response.

2. In patients with high P-selectin (upper tertile), significantly more cardiovascular events are observed compared to patients with low P-selectin (lower tertile), which makes it possible to use the P-selectin level to estimate the prognosis in patients with stable angina.

3. The data obtained in the study allow in the long term to use a new biomarker of inflammation of P-selectin to estimate the prognosis in patients with stable angina and to personalize therapy of patients with coronary heart disease aimed at reducing the «residual» cardiovascular risk associated with the activation of various mechanisms of the systemic inflammatory response.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study the level of P-selectin drug in patients with stable angina with correction of the frequency and doses of antiplatelet agents.

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