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INFLUENCE OF NON-STEROID ANTI-INFLAMMATORY DRUGS ON THE HEMOSTASIS SYSTEM IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

The greatest medical, social and economic burden on society is primarily associated with rheumatoid arthritis (RA). The desire to improve the quality of life of RA patients sometimes justifies lifelong prescription of non-steroid anti-inflammatory drugs (NSAIDs). However, NSAIDs have a number of undesirable reactions, among which, in the last decade, complications from the cardiovascular system (CVS) have been given the greatest importance. Monitoring of the side effects of NSAIDs used in everyday practice is an urgent problem in modern medicine. This problem is especially relevant in rheumatic diseases, in which the systemic inflammatory process is associated with an increased risk of vascular accidents.

Keywords: Rheumatoid Arthritis, Coronary Heart Disease, Non-Steroidal Anti-Inflammatory Drugs, Platelet Aggregation.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immunoinflammatory disease characterized by progressive destruction of joints and damage to internal organs, which is based on disturbances in the humoral and cellular immune system [1, 2, 3]. In the absence of effective therapy, life expectancy in patients with RA is lower by 3 years in women and 7 years in men, primarily due to the high risk of developing comorbid diseases [4]. Rheumatic diseases are reasonably considered by the medical community as risk factors for the development of severe concomitant chronic conditions, which often result in fatal disasters (myocardial infarction, stroke, thrombosis of other large vessels, acute and chronic renal failure, etc.) [23, 24].

It has been established that the hemostatic system, inflammation and innate immunity have a common evolutionary origin, which explains the pathogenetic aspects of the relationship between inflammation and disorders in the hemostatic system [7, 8, 12]. Excessive activation of the hemostatic system can itself maintain inflammatory activity and thus contribute to the progression of dystrophic and destructive changes in organs and tissues.

The pathogenesis of cardiovascular complications is, firstly, associated with the suppression of the synthesis of prostaglandin E2 (PGE2) and prostacyclin. COX-2-dependent synthesis of PGE2 is an important mechanism for controlling blood pressure in conditions of arterial hypertension (AH), and prostacyclin prevents local platelet aggregation in the area of atherosclerotic plaques, providing a powerful antithrombotic effect. Secondly, COX-dependent synthesis of thromboxane A2 (TxA2), which is a stimulator of platelet aggregation and a vasoconstrictor, may be significant in the development of atherothrombosis. The rheological

The Seybold Report
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properties of blood and blood flow in the coronary vessels depend on the quantitative ratio of these hormones. Consequently, NSAIDs play an important role in the regulation of vascular homeostasis and can cause destabilization of hypertension and promote the development of vascular thrombosis [5, 6]. According to large cohort studies, cardiovascular mortality ranges from 15 to 50% [9,-11, 15]. It has been proven that there is a close connection between the progression of atherosclerotic vascular damage and the hyperproduction of proinflammatory mediators and autoantibodies, in particular, rheumatoid factor (RF) and antibodies to citrullinated proteins (ACP), the hyperproduction of which in RA is associated with the synthesis of prothrombotic and proinflammatory mediators, oxidative stress and, as a consequence, high risk of cardiovascular mortality [13, 14].

Consequently, the development of cardiovascular complications in RA is due to the accumulation of traditional risk factors, the presence of chronic inflammation, and side effects of ongoing antirheumatic therapy [15].

Aim of the study was study of the cellular and vascular components of hemostasis in patients with RA and assessing of the nature of the effect of a selective and non-selective COX-2 inhibitor on the state of hemostasis.

MATERIALS AND METHODS

102 patients with RA were observed (86 women (84.3%), 16 men (15.7%). The average age of the patients was 42.3 +1.1 years. The duration of the disease is from 1 to 25 years. The control group, comparable to the main group in age and gender, included 16 healthy volunteers. Diagnosis of RA was carried out in accordance with the American Association of Rheumatology (AAR) and the European League of Rheumatology (EULAR). RA activity was assessed using the DAS28 scale. All patients underwent a clinical examination, a complete blood count was determined, and at the same time, activated partial thromboplastin time (aPTT), prothrombin index (PTI), and fibrinogen were examined in patients with RA using a Rayto RT-2201 C hemostasis analyzer (China). The study of platelet aggregation was carried out on an ALAT2-Biola laser platelet aggregation analyzer, model LA 230-2, using the light transmission fluctuation (LTF) method. Adenosine diphosphate (ADP; 5 and 1.25 μg/ml) was used to perform the hemolysate aggregation test (HAT). The level of von Willebrand factor in blood plasma was studied using a laser platelet aggregation analyzer ALAT2-Biola, model LA 230-2. The number of platelets in peripheral blood was determined according to Fonio, platelet morphology was studied using the Shitikova method. 79 (77.5%) patients were diagnosed with articular form and 23 (22.5%) with articular-visceral form. All subjects had a slowly progressive course of the disease. The activity of the I degree was observed in 30 (24.9%), II - in 53 (52%), III - in 19 (18.6%) patients. I stage of X-ray was observed in 7 (6.9%), II stage - in 31 (30.4%), III stage - in 42 (41.2%) and IY stage in 22 (21.5%) patients. I degree of functional failure was indicated in 16 (15.7%) patients, II degree - in 70 (68.6%), III degree - in 11 (10.8%) patients with RA, only in 5 (4.9 %) of patients functional ability was preserved. To study the effect of various representatives of NSAIDs on the state of the cellular and vascular components of the hemostasis system, all patients were divided into 3 groups. I group

The Seybold Report
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was consisted of 36 (35.3%) patients with RA who received non-selective NSAIDs (Naproxen 250 mg 2 times a day), II group - 32 (31.4%) were represented by patients who received selective NSAIDs against the background of basic therapy (Nimesil 100 mg 2 times a day), III group - 34 (33.3%) patients who took selective and non-selective NSAIDs as part of complex treatment. Patients of the three groups were comparable in gender, age, duration and degree of disease activity. The obtained data were processed by the method of variation statistics using standard application packages Microsoft Excel and Statistica 6.0. Significance of differences was accepted at $P<0.05$.

RESULTS OF THE RESEARCH AND DISCUSSION

Chronic inflammation stimulates platelet turnover in the bone marrow, promoting an increase in the number of reticulated platelets, which have a spherical shape, increased size and pseudopodia [16-18]. These platelets produce proteins that induce blood clots and platelet-derived growth factor [19, 20]. Violation of the relationship between thrombogenic potential and thromboresistance of the vascular wall in patients with RA can act as an important pathogenetic link in the immune-inflammatory process and the associated progression of degenerative-destructive changes in the joints.

Moreover, the high risk of developing intravascular thrombosis in RA can significantly affect the effectiveness of therapy. Since drugs from the NSAID group themselves have a modifying effect on the qualitative and quantitative parameters of hemostasis. The results of studies conducted in this area showed that with the use of naproxen, the content of inactive disc-shaped platelets (discocytes) in the peripheral blood does not change significantly, nimesil tends to increase, and combination therapy significantly increases by 14.2%, ($P< 0.05$) and becomes higher than in the control group (Table 1). The proportion of “abnormal” forms of platelets such as discoechinocytes, spherocytes and spheroechinocytes under the influence of naproxen decreases compared to the initial values by only 9.9%, 16.5% and 16%, respectively.

Almost similar changes were noted during treatment with nimesil. In patients receiving a combination of non-selective and selective COX-2, changes in the specific gravity of activated forms of platelets were more pronounced, so the specific gravity of discoechinocytes decreased by 47.7%, spherocytes by 50% and spheroechinocytes by 61.4%. Along with this, against the background of combination therapy, the sum of activated forms of platelets and the number of platelets involved in aggregates decreases compared to the baseline, respectively, by 47.6% and 47.7%. Studies of the functional activity of platelets indicate that during treatment with these drugs, the number of platelets in the peripheral blood does not change significantly compared to the initial data. However, with combined treatment, there was an increase in these cells by 22.4% compared to the values before treatment (Table 1).

The Seybold Report
ISSN 1533-9211

Table 1: Morphology and functional activity of platelets in patients with RA before and after treatment

Indicators	Healthy	Before treatment	Naproxen	Nimesil	Combination therapy
			After treatment	After treatment	After treatment
Discocytes (%)	84,3±3,52	72,3±1,53*	75,6±2,14**	76,4±1,73**	82,6±3,0**
Discoechinocytes (%)	11,2±0,91	19,9±0,43*	18,1± 0,93**	17,8± 0,71**	12,4± 0,92**
Spherocytes (%)	1,6±0,22	4,2 ±0,1*	3,51± 0,52	3,68± 0,14**	2,1± 0,1**
Spheroechinocytes (%)	1,2±0,13	4,4 ±0,2*	3,7± 0,25**	3,23± 0,09**	1,7± 0,1**
Platelet count in peripheral blood (10 (9)/l)	228,6±11,9	179,4±6,07*	197,0±5,29	219,6±5,59**	285,0±5,37**
Number of platelets involved in aggregates	7,12±0,5	13,8±0,36*	11,4± 0,41**	12,11±0,24**	8,6± 0,4**
Sum of active forms of platelets %	12,9±0,79	27,9±0,61*	25,0± 0,87**	20,0± 0,71**	14,6± 0,62**
Hemolysate aggregation test (II dilution/sec)	14,3±0,92	8,5±0,32*	8,83±0,48	9,3±0,52**	19,2±0,44**
Hemolysate aggregation test (VI dilution/sec)	35,2±1,54	19,2±0,66*	21,4±1,19**	20,1±1,25**	36,6±1,15**

*Note. * P<0.05 compared with control; **P<0.05 compared with data before treatment*

The duration of the hemolysate aggregation test in dilution II with the use of naproxen increases only by 4% compared to the initial data, and with nimesil - by 9.4%. The duration of the hemolysate aggregation test in dilution VI against the background of naproxen is extended by 11.5% and only by 4.7% in the nimesil group, compared with that of the control group. There is a tendency that the NSAIDs used differ in their effect on the functional activity of platelets. Thus, naproxen has a predominant effect on the aggregation ability of platelets, and nimesil has a predominant effect on the ability of platelets to adhesion. Under the conditions of combined treatment of RA patients, there is a significant increase in the time of the hemolysate aggregation test in dilutions II and VI by 1.55 and 1.91 times, respectively, compared with those before treatment.

It is known that there is a dynamic balance between the cellular and vascular components of hemostasis under physiological conditions. The development of an imbalance in these systems will undoubtedly lead to disruption of hemostasis. When using naproxen, there is a significant increase in activated recalcification time (AVR) by 21.3% and activated partial thromboplastin time by 9.7% (Table 2). There is a decrease in the prothrombin index, fibrinogen, plasma tolerance to heparin, and an increase in the fibrinolytic activity of the blood by 1.87 times. When using nimesil, there is no significant change in the activated recalcification time and activated partial thromboplastin time compared to the initial values. There is a slight decrease in the prothrombin index and plasma fibrinogen. Fibrinolytic activity and fibrin-stabilizing factor of blood plasma do not undergo significant changes. However, there is a decrease in plasma tolerance to heparin by 19.5% compared to the initial data. When combining NSAIDs, the activated recalcification time and the partially activated thromboplastic time are extended

The Seybold Report
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by 37.2 and 46.7%, respectively. The prothrombin index also decreases noticeably. With the combined use of NSAIDs, the level of plasma fibrinogen, compared with the levels before treatment, decreases by 37.5%, and fibrinous activity by 25.7%. The fibrinolytic activity of blood plasma increases almost 2 times. Plasma tolerance to heparin decreases by 36.1% (Table 2).

Table 2: Indicators of the coagulation link of the hemostatic system in patients with RA before and after treatment

Indicators	Healthy	Before treatment	Naproxen	Nimesil	Combination therapy
			After treatment	After treatment	After treatment
Activated recalcification time (sec)	63,0±3,24	48,4±1,21*	58,7±176**	45,6±2,42**	66,4±3,13**
Activated partial thromboplastin time (sec)	37,9±1,67	28,7±0,94*	31,3±0,56	29,8±1,28**	42,1± 1,32**
Prothrombin time%	90,0±2,56	106,1±3,84*	81,4± 3,71	98,6± 2,81**	90,8± 3,03**
Fibrinogen content g/l	2,6±0,29	5,4±0,17*	3,0±0,18	4,4± 0,27**	3,7± 0,25**
Fibrinolytic activity %	0,91±0,06	0,41±0,03*	0,77±0,05**	0,4±0,03**	0,79±0,04**
Fibrin stabilizing factor %	88,9±3,05	66,9±1,86*	64,2± 3,33	81,4± 2,41**	85,1±2,46**
Plasma tolerance to heparin	8,1±0,54	16,9±0,54*	13,4±0,4	13,6± 0,36**	10,8± 0,3**

*Note. * P < 0.05 compared with control; **P <0.05 compared with data before treatment*

Thus, in patients with RA, while using NSAIDs, the vascular part of the blood coagulation system also undergoes changes. One of the main manifestations of the imbalance between the thrombogenic potential and thromboresistance of the vascular wall is a decrease in the synthesis of prostacyclin and an increase in the production of thromboxane [12]. An increase in the functional activity of platelets leads to activation of the plasma coagulation mechanism of thrombinemia against the background of depletion of the fibrinolytic and anticoagulant systems, which contributes to the development of DIC syndrome. NSAIDs, by blocking the activity of COX, alter the production of prostocycline and thromboxane [21, 22]. Apparently, it is this mechanism of action of NSAIDs that underlies the changes we obtained in the cellular and vascular components of hemostasis. Thus, we can conclude that in conditions of RA, disturbances occur in both the quantitative and qualitative characteristics of platelets and their functional activity. Changes in the cellular part of hemostasis in patients with RA develop against the background of failure of the vascular part of hemostasis.

The Seybold Report
ISSN 1533-9211

CONCLUSIONS

1) Shifts in the hemostatic system in RA are hypercoagulable in nature.
2) The combined use of two NSAIDs has an undoubted advantage over monotherapy, both in terms of clinical effectiveness and influence on the hemostatic system. However, to reduce the risk of developing both hypercoagulable and hypocoagulable complications, monitoring of blood coagulation parameters is required.

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The Seybold Report
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