ВЛИЯНИЕ ТЕРАПИИ ДЕКСАМЕТАЗОНОМ НА ФАКТОРЫ АДГЕЗИВНОСТИ И КОАГУЛЯЦИИ ПРИ ОСТРОЙ ИШЕМИИ НИЖНИХ КОНЕЧНОСТЕЙ

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Резюме. Лейкоцитарно-тромбоцитарная адгезия при гипоксии, повреждении тканей, активации воспаления и коагуляции ассоциирована с экспрессией мембранных молекул ICAM-1 и интегринов клетками крови и тканей. Одновременно адгезионные рецепторы тромбоцитов обусловливают их адгезию к эндотелию и к рекрутированным лимфоцитам. Роль тромбоцитов в патогенезе ишемических сердечно-сосудистых заболеваний также состоит в их способности модулировать как реакции гемостаза, так и воспалительные реакции, что сопровождается секрецией воспалительных медиаторов и факторов, способствующих рекрутированию лейкоцитов в места повреждения тканей. Цель исследования – изучить влияние синтетического глюкокортикоида дексаметазона на экспрессию адгезионных рецепторов $CD18^+$ и $CD54^+$ на лейкоцитах, содержание тромбоцитов и фибриногена в крови пациентов с ОИНК, связь этих показателей с тяжестью течения и исходом заболевания.

Для изучения влияния противовоспалительной терапии сформирована группа из 32 пациентов с терапией дексаметазоном; группа сравнения представлена 71 пациентом с базисной терапией, контрольную группу составили 15 волонтеров. После операции реваскуляризации все больные получали дезагрегантную и антикоагулянтную терапию. Инфузии дексаметазона проводили курсом от 4 до 6 дней после реконструктивной операции. У всех пациентов определяли содержание С-реактивного белка в крови, содержание тромбоцитов и фибриногена. С помощью иммуноцитохимического метода подсчитывали число лимфоцитов, экспрессирующих молекулы адгезии ICAM-1 ($CD54^+$) и интегрины ($CD18^+$). Исследования выполняли до операции и на 1-е, 3-и, 7-е, 10-е сутки после операции.

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При обострении ишемии и повреждении эндотелия, накоплении продуктов цитолиза усиливается экспрессия молекул адгезии как на эндотелиоцитах, так и на клетках-эффекторах воспаления – лейкоцитах и тромбоцитах. Молекулы адгезии проводят активационный сигнал внутрь клетки, что способствует адгезии лейкоцитов и тромбоцитов к эндотелию, лимфоцитарно-тромбоцитарной адгезии, образованию пристеночного тромба и возможной окклюзии поврежденных сосудов. Усиление экспрессии молекул адгезии связано с активацией метаболизма, воспаления, коагуляции и оксидативного стресса, стимулирует все ростки кроветворения, в том числе тромбоцитарный. Уровень вовлечения клеточных реакций в патогенез заболевания влияет на эффективность и продолжительность лечения, риск рецидивов тромбоза и летального исхода. Противовоспалительная терапия с дексаметазоном способствовала более ранней ремиссии, снижению доли инфекционных осложнений, таких как нагноение ран с 10% до 6%, количества необходимых ампутаций с 32% до 16%, частоты летальных исходов с 31% до 6%, сокращению сроков пребывания в стационаре с 13 дней до 10.

Воспаление, адгезивность клеток-эффекторов и тромбоз являются важными факторами патогенеза острой ишемии нижних конечностей. Терапия дексаметазоном способствует снижению уровня системного воспалительного ответа, количества необходимых ампутаций, числа осложнений и неблагоприятных исходов при лечении ОИНК, сокращению сроков пребывания в стационаре.

Ключевые слова: острая ишемия нижних конечностей, молекулы адгезии, фибриноген, тромбообразование, дексаметазон

EFFECT OF DEXAMETHASONE THERAPY ON FACTORS OF ADHESIVENESS AND COAGULATION IN ACUTE LOWER LIMB ISCHEMIA

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Abstract. Leukocyte-platelet adhesion during hypoxia, tissue damage, activation of inflammation and coagulation is associated with the expression of ICAM-1 membrane molecules and integrins by blood and tissue cells. At the same time, platelet adhesion receptors determine their adhesion to the endothelium and recruited lymphocytes. The role of platelets in the pathogenesis of ischemic cardiovascular diseases also consists in their ability to modulate both hemostasis and inflammatory reactions, which is accompanied by the secretion of inflammatory mediators and factors that promote the recruitment of leukocytes to tissue damage sites. Purpose of the study: to study the effect of the synthetic glucocorticoid dexamethasone on the expression of adhesion receptors $CD18^+$ and $CD54^+$ on leukocytes, the content of platelets and fibrinogen in the blood of patients with ALLI, the relationship of these indicators with the severity and outcome of the disease.

To study the effect of anti-inflammatory therapy, a group of 32 patients treated with dexamethasone was formed; the comparison group was represented by 71 patients with basic therapy, the control group consisted of 15 volunteers. After revascularization, all patients received antiplatelet and anticoagulant therapy. Dexamethasone infusions were carried out in a course of 4 to 6 days after reconstructive surgery. In all patients, the content of C-reactive protein in the blood, the content of platelets and fibrinogen were determined. The number of lymphocytes expressing adhesion molecules ICAM-1 ($CD54^+$) and integrins ($CD18^+$) was counted using the immunocytochemical method. Studies were performed before surgery and on days 1, 3, 7, and 10 after surgery.

With exacerbation of ischemia and damage to the endothelium, the accumulation of cytolysis products, the expression of adhesion molecules increases both on endotheliocytes and on inflammatory effector cells – leukocytes and platelets. Adhesion molecules conduct an activation signal inside the cell, which promotes adhesion of leukocytes and platelets to the endothelium, lymphocytic-platelet adhesion, the formation of a

parietal thrombus, and possible occlusion of damaged vessels. Increased expression of adhesion molecules is associated with the activation of metabolism, inflammation, coagulation and oxidative stress, stimulates all hematopoietic lineages, including platelets. The level of involvement of cellular reactions in the pathogenesis of the disease affects the effectiveness and duration of treatment, the risk of recurrent thrombosis and death. Anti-inflammatory therapy with dexamethasone contributed to earlier remission, a decrease in the proportion of infectious complications, such as wound suppuration from 10% to 6%, the number of necessary amputations from 32% to 16%, the frequency of deaths from 31% to 6%, and a reduction in hospital stay from 13 days to 10.

Inflammation, adhesiveness of effector cells and thrombosis are important factors in the pathogenesis of acute lower limb ischemia. Therapy with dexamethasone helps to reduce the level of systemic inflammatory response, the number of necessary amputations, the number of complications and adverse outcomes in the treatment of ALLI, and reduce the length of stay in the hospital.

Keywords: acute lower limb ischemia, adhesion molecules, fibrinogen, thrombus formation, dexamethasone

Introduction

Thrombogenesis underlies a number of diseases of the cardiovascular system (cerebral stroke, myocardial infarction, damage to the vessels of the extremities, kidneys, etc.) and is currently the main cause of death in industrialized countries. The leading component of the pathogenesis of vascular diseases is endothelial dysfunction, and thrombosis in arterial vessels is mainly based on activation of the vascular-platelet link of hemostasis. The cessation of blood flow due to blockage of the vessel by a thrombus leads to the development of acute lower limb ischemia (ALLI). Currently, the most effective method of revascularization in patients with ALLI is the surgical method, however, this does not eliminate the main cause of the disease [14]. One of the most common postoperative complications are retromboses and restenoses in the area of vascular reconstruction due to neointimal hyperplasia, as well as general hemodynamic disorders and disorders of the blood coagulation system [12].

In patients with ALLI, obviously, vascular occlusion is the result of activation of chronic inflammation of the vascular wall, increased adhesive properties of blood leukocytes and endothelium, tissue ischemia. Recirculation and recruitment of leukocytes in the area of inflammation is mediated by a specific ligand-receptor interaction between adhesion molecules of endotheliocytes, platelets and leukocytes, the expression of which is regulated by inflammatory mediators and cytokines. Membrane molecules involved in lymphocytic-platelet adhesion are ICAM-1 (Intercellular adhesion molecule, $CD54^+$), expressed by blood and tissue cells [12].

Adhesion molecules that mediate leukocyte-endothelial interactions undergo complex changes in patients treated for ALLI. Both postischemic reperfusion and the particular treatment chosen seem to influence the expression of adhesion molecules, which include ICAM-1, selectins, and integrins.

Integrins are a large family of cell surface molecules found on cells of various tissues. Integrins mediate the interaction of cells with their microenvironment, providing cell-to-cell and cell-to-matrix adhesion. Integrins are heterodimers of glycoproteins, consisting of various combinations of a- and J-chains. Expressed on leukocytes: CD18 as part of lymphocyte function associated antigen-1 (LFA-1, CD11a), macrophage antigen-1 (Mac-l, CD11b), pl50.95. Ligands for LFA-1 are: ICAM-1 ($CD54^+$), ICAM-2, ICAM-3, for Mac-l ICAM-1. These integrins mediate adhesion to the endothelium of neutrophils, basophils, eosinophils, monocytes, and lymphocytes.

The αMβ2 leukocyte integrin (CD11b/CD18, Mac-1) is also a high-affinity fibrinogen receptor on stimulated macrophages, monocytes, and neutrophils.

The function of inflammatory CAMs can be modulated by several mechanisms, including competitive blockade, altered cell surface expression, and, for integrins, interference with receptor activation. The ultimate therapeutic goal of each is to interrupt the multi-step recruiting cascade. In clinical practice, several groups of pharmaceuticals are used that directly or indirectly affect the function of CAMs [13]. For example, inhibition of IL-1β or TNFα by antibodies or soluble receptors has a powerful effect on the expression of CAMs on endothelial cells. Moreover, corticosteroids, non-steroidal anti-inflammatory drugs, and antioxidants also reduce the expression of inflammatory CAMs and chemokines, at least in part, by blocking the function of the inflammatory nuclear transcription factor κB (NF-κB) [5, 10].

In an experimental model, Mac-1 and CD18 knockout mice show reduced infarct volume and lower mortality after cerebral ischemia/reperfusion [6]. Immunoblockade of CD11b, CD18 or Mac-1 also protects the brain from ischemic damage [5]. In addition, CD18 immunoblockade reduces leukocyte recruitment while reducing cerebral edema and infarct size [4, 6].

Blocking CAMs that mediate leukocyte accumulation during inflammation is considered an effective strategy for the treatment of clinical

inflammatory diseases. However, despite promising preclinical results, results from clinical trials have been inconsistent. With the exception of some positive effects in psoriasis and asthma, prevention of either selectin or CD18 β2-integrin activity has had a limited effect, especially in the treatment of ischemia-reperfusion injury [2].

The common chain β2 integrin (CD18) is a major target for modulating innate immunity, and blocking this pathway has a profound effect on neutrophil adhesion and accumulation in acute inflammation [6]. However, clinical trials of CD18-blocking monoclonal antibodies (mAb) Rovelizumab and Erlizumab (LeukArrest™) were unsuccessful in reducing myocardial or brain ischemic injury [1, 4]. Moreover, a mAb against ICAM-1, CD54 (Enlimomab), the main counter-receptor for CD18 on leukocyte and endothelial cells, even had a negative effect in a phase II study in stroke [11]. The study highlights that blocking the effects of inflammatory CAMs may be of limited use in the treatment of ischemic injury. The use of monoclonal antibodies to prevent thrombosis did not lead to the desired clinical result, because radical inhibition of leukocyte adhesion to the endothelium led to undesirable side effects (development of infections, death [1, 11]).

The aim of the study was to study the effect of the synthetic glucocorticoid dexamethasone on the expression of adhesion receptors $CD18^+$ and $CD54^+$ on leukocytes, the content of platelets and fibrinogen in the blood of patients with ALLI, the relationship of these parameters with the severity of the course and outcome of the disease.

Materials and methods

To achieve the goal, 2 groups of patients were formed: the main one, in which, against the background of basic therapy, dexamethasone (DM) was administered intravenously at a dose of 8 mg in 200 ml of isotonic sodium chloride solution for 4-6 days after reconstructive surgery, 32 patients, age 76 (70-81) years; comparison group – 71 patients with basic therapy, age 70 (64-83) years. Basic therapy (BT) included painkillers, antibacterial, antiplatelet, anticoagulant agents. Patients with uncompensated ischemia underwent revascularization; patients with irreversible ischemia underwent revascularization to reduce the level of amputation; the volume of surgical intervention was to perform an embolectomy followed by a large amputation. The control group is represented by practically healthy volunteers, aged 70 (55-80) years.

The studies were performed before surgery upon admission to the hospital and on days 1, 3, 7, and 10 after surgery. In all patients, the blood levels of C-reactive protein (CRP) as an inflammation marker, creatine kinase activity (Cobas 6000 C501, Switzerland), the number of platelets – PLT and large platelets – P-LCR – (SYSMEX XT4000i, Japan), the relative content of $CD18^+$ and $CD54^+$ mononuclear leukocytes by immunocytochemical method (Novocastra, UK), fibrinogen content in blood (StaCompact Plus, France). To assess comorbidity, the Charlson M.E. index was used. [3]. The level of systemic inflammatory response (SIRS) was determined using the criteria adopted at the ACCP/SCCM consensus conference in 1992 (USA). The result of treatment was determined by the length of stay in the hospital and the outcome of the disease: good (4) – discharge after 7 days and earlier; satisfactory (3) – treatment for more than 7 but less than 14 days; unsatisfactory (2) – treatment for more than 14 days; bad (1) – death. Statistical processing was performed by the methods of variation statistics (Statistica 6.0): the median (Me) and percentiles ($Q_{0.25}$-$Q_{0.75}$), Spearman's correlation coefficient, Student's t-test were determined. The critical significance level (p) of statistical hypotheses was taken as 0.05.

Results and discussion

In the period of acute ischemia (before surgery), 51% of patients with basic therapy developed SIRS (2 or more signs), in the reperfusion period, SIRS was registered in 53% of patients, and in 10% the degree of SIRS increased to 4 signs (Table 1). In patients treated with DM, SIRS was noted in 47% of patients on admission; in the reperfusion period, SIRS decreased to 27%. Thus, the reduction in the degree of systemic inflammation is more pronounced in the treatment of DM. The level of systemic inflammatory response in the acute period (at admission before surgery) had a high predictive value for the outcome of the disease (AUC = 0.88; sensitivity 88%, specificity 75%); during the reperfusion period, an increase in the systemic inflammatory response leads to an unfavorable outcome (predictive value AUC = 0.93; sensitivity 89%, specificity 92%).

In all patients, chronic cardiovascular diseases prevailed in the structure of comorbidity. The mean Charlson comorbidity index in patients treated with BT + DM was 10.0 points; in patients with BT – 9.9 points, in volunteers of the control group – 6.7 points. The concentration of CRP in the blood of all patients upon admission to the hospital exceeded normal values by 11-14 times and reached a maximum in the period of reperfusion, that is, on days 3-7 after surgery (Table 2). In patients treated with DM, the concentration of CRP decreased by the 7th day of observation and was 2 times lower than in the comparison group.

Receptors involved in lymphocyte-platelet adhesion are ICAM-1 ligands for β2-integrins (CD11a/CD18, CD11b/CD18), LFA-1, Mac-1, and CD43 [9]. The content of cells carrying integrins was increased in all patients during the period of acute

ischemia, after thrombectomy, the number of $CD18^+$ and $CD54^+$ began to gradually decrease, but only in patients receiving dexamethasone infusions, these parameters normalized by day 7 of the disease (Table 2).

In all patients with ALLI, the content of $CD54^+$ lymphocytes correlated with the outcome of ALLI before thrombectomy ($r = -0.652$, $p < 0.05$) and during reperfusion ($r = -0.956$, $p < 0.05$). The number of these cells is associated with the activity of inflammation, as evidenced by the correlation with the concentration of CRP ($r = 0.952$; $p < 0.01$) and the number of large (immature) platelets ($r = -0.845$; $p < 0.001$). An increase in the content of large platelets is also associated with the number of $CD18^+$ mononuclear cells ($r = 0.563$; $p < 0.001$).

The content of fibrinogen in the blood of patients with ALLI at admission increased 1,3 times compared with the concentration in practically healthy people. In the period of reperfusion, the products of necrosis and cytolysis accumulated as a result of vessel occlusion are washed into the bloodstream and contribute to the activation of inflammation, oxidative stress [7, 8], and coagulation. Strengthening the coagulant properties of blood is accompanied by the risk of thrombosis, which can also occur in other problematic vascular areas (myocardial infarction, acute cerebrovascular accident). For this period, patients with ALLI are characterized by a continuing increase in the concentration of fibrinogen in the blood (Table 2), which leads to an increase in viscosity, and, consequently, a slowdown in blood flow and the risk of rethrombosis.

TABLE 1. RATIO OF THE NUMBER OF SIGNS OF SIRS IN PATIENTS WITH DIFFERENT THERAPIES IN THE ACUTE PERIOD AND THE PERIOD OF REPERFUSION

Type of therapy	Disease period	Number of SIRS signs in the group (%)				
		0	1	2	3	4
Basic therapy	Acute ischemia	13	36	31	20	0
	Reperfusion period	19	28	23	20	10
Dexamethasone therapy	Acute ischemia	13	40	29	18	0
	Reperfusion period	33	40	20	7	0

TABLE 2. FACTORS OF ADHESIVENESS AND THROMBOSIS IN PATIENTS WITH ACUTE ISCHEMIA OF THE LOWER EXTREMITIES WITH DIFFERENT THERAPY

Terms of observation	Patients with basic therapy					Patients with therapy dexamethasone				
	CRP (mg/L)	$CD18^+$ (%)	$CD54^+$ (%)	Plt (10^9/L)	fibrinogen (g/L)	CRP (mg/L)	$CD18^+$ (%)	$CD54^+$ (%)	Plt (10^9/L)	fibrinogen (g/L)
Before surgery	41* (9-86)	59 (48-62)	32* (23-41)	246 (171-283)	4.9* (4.3-5.8)	35* (8-52)	65* (55-72)	29* (25-40)	255 (180-329)	4.4* (4.3-5.2)
After surgery	67* (31-156)	57* (54-68)	25* (21-34)	229 (154-279)	4.8* (4.2-5.3)	62* (19-86)	56 (50-71)	24 (14-31)	241 (179-322)	5.2* (3.4-6.1)
3rd day	108* (52-157)	66* (53-73)	24 (19-27)	350* (298-409)	6.1* (5.2-7.1)	71* (13-81)	60 (34-73)	20 (14-24)	295 (202-351)	5.9* (5.2-6.0)
7th day	62* (21-135)	78* (76-80)	15* (9-18)	421* (341-516)	7.2* (6.1-8.3)	28* (15-34)	42# (34-52)	9* (5-16)	299# (234-362)	6.2* (4.4-8.5)
10th day	74* (51-141)	66 (56-69)	26* (22-31)	324 (257-340)	7.2* (6.0-7.3)	31*# (22-39)	42# (34-49)	17# (14-23)	282 (202-360)	5.1# (5.0-6.0)
Control	3 (1-4)	49 (46-53)	19 (15-22)	227 (189-258)	3.7 (3.5-4.0)	3 (1-4)	49 (46-53)	19 (15-22)	227 (189-258)	3.7 (3.5-4.0)

Note. *, differences from the control group; #, differences between groups of patients; $p < 0.05$.

When using DM infusions, we observed a decrease in the concentration of fibrinogen by the 10th day of observation to the reference values. In patients receiving basic therapy, the fibrinogen level increased from the 3rd day after the operation and remained elevated up to 10 days despite the ongoing anticoagulant therapy (Table 2). That is, with standard therapy in patients with ALLI, along with persistent clinical and laboratory signs of inflammation activity, the level of fibrinogen and platelets remains elevated, which indicates the importance of limiting inflammation in the treatment of ALLI. The use of additional anti-inflammatory therapy contributed both to the onset of remission of ALLI, combined with a significant decrease in the level of fibrinogen and platelets, the number of leukocytes expressing adhesion receptors.

The activity of creatine kinase as a marker of cytolysis in ischemic tissues also significantly increased upon admission of patients and reached 1600-2500 U/L (in healthy volunteers 76 (65-97) U/L). In patients with DM therapy, the activity of this enzyme returned to normal by day 5, in patients with BT, only by day 7 after surgery.

Correlation analysis showed that the concentration of fibrinogen in the blood in the acute period is associated with the level of inflammation (leukocyte level: $r = 0.952$, $p < 0.05$, SIRS: $r = 0.910$, $p < 0.05$, CRP: $r = 0.995$, $p < 0.05$), cytolysis ($r = 0.985$, $p < 0.05$), chemiluminescence of blood leukocytes ($r = 0.909$, $p < 0.05$), ALT activity $r = 0.943$, $p < 0.05$. Also, a high concentration of fibrinogen creates a risk of a lethal outcome of the disease ($r = -0.914$, $p < 0.05$). In the reperfusion period, the fibrinogen level also maintained a correlation with the CRP level ($r = 0.651$, $p < 0.05$), platelet count ($r = 0.586$, $p < 0.05$), leukocyte chemiluminescence ($r = 0.921$, $p < 0.05$). On the 10th day of the disease, the correlation with the above indicators remained. In the acute period and in the reperfusion period, the platelet count in the blood correlated with creatine kinase activity ($r = 0.634$, $p < 0.01$) and creatinine level ($r = -0.465$, $p < 0.05$), which demonstrated the importance of cytolysis for the involvement of the renal glomeruli in the pathological process with ALLI. $CD18^+$ correlates with the content of large platelets ($r = 0.719$, $p < 0.001$), which also increases the risk of acute renal failure, since, due to their size, large platelets do not easily cross the renal tubules.

Evaluation of treatment outcomes is shown in Picture1. The method of treatment using dexamethasone allowed not only to improve the results of postoperative treatment of patients with acute ischemia of the lower extremities, but also to reduce mortality from 31% with basic therapy to 6%, the incidence of complications: gangrene of limb tissues from 30% with BT to 6%; sepsis from 10% to 6%; wound suppuration from 10% to 6%, respectively. Treatment with dexamethasone reduces the number of amputations from 32% in patients with basic therapy to 16%, and reduces the duration of treatment for patients discharged from the hospital from an average of 13 to 10 bed-days.

1. Predictors of early postoperative mortality are: an increase in the content of leukocytes expressing $CD18^+$% adhesion molecules (according to ROC analysis, predictive value: AUC = 0.82; sensitivity 70%, specificity 70%); development of a systemic inflammatory response (predictive value: AUC = 0.88; sensitivity 88%, specificity 75%); comorbid status (AUC = 0.80; sensitivity 78%, specificity 72%).

2. In the reperfusion period, the predictors of an unfavorable outcome are an increase in the content of leukocytes expressing $CD54^+$% adhesion molecules ($r = -0.956$, $p < 0.05$), an increase in the systemic inflammatory response (AUC = 0.93, sensitivity 89%, specificity 92%) and comorbid status ($r = -0.361$, $p < 0.001$).

Conclusions

Therapy with dexamethasone helps to reduce the level of systemic inflammatory response, the number of required amputations (from 32% to 16%), the number of complications and adverse outcomes in the treatment of ALLI (from 32% to 6%).

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