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INVESTIGATION OF HEMATOTOXIC EFFECT OF MICRO- AND NANOPARTICLES OF IRON OXIDE Fe_2O_3 UNDER SINGLE AND LONG-TERM INTAKE INTO THE BODY

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Introduction. Due to its specific magnetic properties, iron oxide nanoparticles (Fe_2O_3 NPs) are used in industry as catalysts, as well as in medicine for the cancer diagnosis and treatment. Given the small size of NPs and their increased biological activity, accumulation in organs as well as slow elimination, the study of their effect on the body is an important medical and biological problem.

The aim of the study was to study the influence of colloidal solutions of iron oxide Fe_2O_3 with micro- and nanoparticles on the composition and coagulometric indices of peripheral rats in the simulation of acute and subchronic intoxication.

Materials and methods of research. The object of the study consists in Fe_2O_3 solutions with particles of 19 nm and 400 nm; male Wistar rats (n = 30), which were divided into 3 groups (n = 10). The 1st experimental group of rats was injected with a solution of Fe_2O_3 NPs 19 nm; 2nd group – Fe_2O_3 solution with particles of 400 nm; the control group of animals was injected with 0.9 % saline. Determination of the peripheral blood composition was performed using a hematology analyzer Elite 3 (Czech Republic), coagulogram indicators on the device Humaclot Junior (Germany). The study was performed after a single intratracheal and 30 times intraperitoneal injections of Fe_2O_3 solutions.

Results. It was found that a single intratracheal injection of colloidal Fe_2O_3 solutions caused changes in hematological parameters (decreased hemoglobin, decreased erythrocytes and platelets, hematocrit, leukocytes, increased monocytes), indicating impaired hematopoiesis and hemoglobin synthesis. The prolonged intoxication with Fe_2O_3 particles led to a significant decrease in the total number of erythrocytes and leukocytes due to the damage of hematopoietic organs, which combined with disruption of hemoglobin synthesis can lead to anemia. Both acute and subchronic intoxication have resulted in changes in platelet cell status and coagulogram, that indicate disorders of the blood coagulation system and a high risk of blood clots.

Conclusions. Acute Fe_2O_3 intoxication caused suppression of erythropoiesis, hemoglobin synthesis and increased blood clotting. Prolonged intake of Fe_2O_3 solutions in rats was characterized by a more distincteffect on all studied blood parameters, which indicates the anemia development, stimulation of macrophage-monocyte cells and increased risk of thrombosis. The obtained data indicate differences in the ability of Fe_2O_3 micro- and nanoparticles to affect the composition of peripheral blood, the process of hemoglobin synthesis and indicators of the blood coagulation system.

Key words: iron oxide, micro- and nanoparticles, peripheral blood, hematotoxicity

Introduction

Among artificially synthesized nanoparticles (NPs) of metal oxides, iron oxide Fe_2O_3 and Fe_3O_4 are the most common by far and are used in industry as catalysts as well as in medicine for the treatment and diagnosis of cancer. Given the special properties of iron oxide NPs, in particular their increased biological activity, accumulation in internal organs and slow elimination, the study of their effects on the state of internal organs and body systems is an important medical and biological problem [1–3].

According to the scientific sources [4–6], the toxic effect of iron oxide NPs depends on both their size and concentration and the route by which they

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enter the body. It was studied that due to the small size, iron oxide NPs can penetrate cell membranes, overcome biological barriers, initiate the formation of reactive oxygen compounds (oxidative stress) and inflammation, damage organoids and DNA, lead to apoptosis and necrosis of cells and tissues. Such properties of magnetic low-frequency iron oxides are not only detrimental to tumor cells, but can also damage cells of normal tissues and organs [7].

One of the sensitive to the action of potentially hazardous chemical factors, in particular heavy metal compounds, is the blood system because they interact with cellular and humoral components of the blood when they enter the body. Consequently, the study of the cellular composition of blood as well as components of the blood coagulate regulation system that provide nonspecific resistance, hemostasis and maintain the fluid state of blood in vessels under the action of iron oxide nanoparticles is very revealing and informative [8, 9].

It was investigated that inhalation of iron oxide particles of sizes 22 and 280 nm in rats at doses of 0.8 and 20.0 mg/kg caused induction of reactive oxygen species in cells, hyperplasia and fibrosis of lung tissue, as well as disruption of the blood coagulation system [5, 6].

Studies performed to assess the effects of ferromagnetic fluid on the vascular system and blood coagulation system using phantom-systems for intravenous drug administration have shown that from the vascular lumen magnetite through the pores in the vascular wall penetrates into the intercellular space, then through the cell membrane inside the cell, where some time is localized on the cell organelles. The study of the system of hemostasis with determination of coagulogram revealed that intravenous administration of magnetite at a dose of 80 mg/kg in weight causes a shift of the coagulation system towards hypercoagulation. At the dose of 125 mg/kg there is a «breakdown» of the hemostasis system and development of dissymmetric intravascular coagulation syndrome [10].

The aim was to study the influence of colloidal solutions of iron oxide Fe_2O_3 with micro- and nanoparticles on the composition and coagulometric indices of peripheral rats in the simulation of acute and subchronic intoxication.

Materials and methods of research

Colloidal solutions of iron oxide Fe_2O_3 with average particle size of 19 nm and 400 nm were the objects of study. Particle size in Fe_2O_3 solutions was determined using a laser particle analyzer Zetasizer NanoZS (Germany).

The experiment was performed on sexually mature male Wistar rats with an initial weight of 260–280 g, which were kept in stationary conditions of the vivarium on a standard food and water regime. The rats were divided into two series, 2 experimental and 1 control group in each (n = 10). The 1st experimental group of rats was injected with Fe_2O_3 NPs 19 nm solution; the 2nd group – solution of Fe_2O_3 with 400 nm particles; the control group was injected with 0.9 % NaCl saline.

When modeling acute intoxication (I series) colloidal solutions of Fe_2O_3 were administered to rats intratracheally in a single dose of 10 mg (iron) per 1 kg body weight. Studies were performed at 21 days after administration. In series II, in the simulation of subchronic intoxication, Fe_2O_3 colloidal solutions were administered 5 times a week at a dose of 1.12 mg (iron) per kg body weight, for a total of 30 injections. Blood was drawn from control and experimental animals after decapitation under thiopental anaesthesia.

All animal manipulations were performed in accordance with the provisions of the «European Convention for the Protection of Vertebrate Animals

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used for experimental and other scientific purposes» (Strasbourg, 1985), and were approved by the Bioethics Committee of the National Academy of Sciences of Ukraine [11].

To determine the effect of iron oxide nanoparticles on peripheral blood hematological studies were performed using an automatic analyzer Elite 3 (Czech Republic), zincprotoporphyrin (ZPP) level in blood was measured using hemofluorimeter 206D (USA) according to the instructions to the device. Determination of blood coagulation parameters (prothrombin time and index, partial thrombin time, plasma fibrinogen content) was performed using a Humaclot Junior coagulometer (Germany) using standard reagent kits. Plasma was isolated from experimental blood (with sodium citrate anticoagulant 3.2 % in a ratio of 9:1) by centrifugation for 10 min at 3000 g before analysis.

Statistical analysis of the obtained data was performed using Microsoft Excel 2010 program. The difference of the indices was registered taking into account Student's t-test and Mann-Whitney U-test [12].

Research results and their discussion

According to literature data [13], the main mechanisms of hematotoxic action of heavy metals are disruption of erythropoiesis, inhibition of heme and globin synthesis (especially α-chain), membrane and cytotoxic effect that leads to reduction of blood cell life span and their morphofunctional changes.

After intratracheal administration to rats of colloidal iron oxide solutions of both sizes particles, a decrease in hemoglobin concentration and an increase in ZPP were observed, indicating a disruption of heme synthesis due to blockage of ferrocholetase and inclusion of zinc instead of iron in the heme composition. In peripheral blood cells a slight decrease of erythrocyte number after Fe_2O_3 400 nm injection (by 9.0 %) and a tendency to a decrease of leukocyte number (by 20.0 %) after Fe_2O_3 19 nm lowers ($p < 0.1$ vs. control) were found. An increase in the percentage of monocytes was observed in both experimental groups of rats as compared with that in the control group (Table 1). Consequently, the results obtained may indicate a slight impairment of erythropoiesis and activation of macrophage-monocytic cells.

It is known that the leading role in maintenance of normal functioning of endothelial cells, implementation of primary hemostasis belongs to thrombocytes. Expressed activation of platelets is the most important trigger mechanism of thrombosis [14].

In our studies we have found that intratracheal administration of colloidal iron oxide solutions to rats of both sizes particles caused a slight increase in platelet count (by 12.6 % and 7.0 % respectively $p < 0.1$) and a significant increase in thrombocrit (by 84.6 % and 61.5 %) and large platelet fraction (by 55.9 % and 47.0 % respectively $p < 0.05$ compared to controls) (Table 1). Since thrombocrit characterizes the percentage of platelet mass in the blood volume and is used to assess the risk of bleeding or thrombosis, the established elevated values of thrombocrit in research rats during administration of Fe_2O_3 NPs can be considered as a sign of the development of vascular thrombosis.

In addition to platelets in the process of fibrin clot formation, blood plasma clotting factors are involved in the cascade of biochemical reactions.

The results showed that after a single intratracheal administration of colloidal solutions of Fe_2O_3 19 nm and 400 nm to the rats, changes in coagulogram parameters were observed in comparison with the control group. In both the 1st and the 2nd experimental groups a significant increase in the level of fibrinogen was detected (by 2.7 and 2.7 times respectively). In the group of animals injected with 400 nm Fe_2O_3 there was found an

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Table 1

Peripheral blood values in rats after a single intratracheal injection of colloidal Fe_2O_3 solutions with 19 nm and 400 nm particles (M ± m, n = 10)

Indexes	Groups of animals		
	Control	Fe_2O_3 19 nm	Fe_2O_3 400 nm
ZPP, mM/M heme	70.75 ± 4.38	135.63 ± 2.58*	70.75 ± 4.38
Hemoglobin, g/l	176.67 ± 2.57	162.50 ± 3.86	160.88 ± 3.64*
Erythrocytes, 10^9/ml	9.86 ± 0.16	9.92 ± 0.81	9.07 ± 0.023#
Hematocrit, %	47.59 ± 0.75	48.80 ± 1.57	47.59 ± 0.75
Leukocytes, 10^6/ml	16.72 ± 0.77	13.36 ± 1.08#	13.83 ± 2.03
Lymphocytes, %	40.38 ± 2.15	44.11 ± 3.26	37.69 ± 4.02
Monocytes, %	10.26 ± 0.62	14.03 ± 1.0#	17.50 ± 4.58*
Neutrophils s/n, %	48.67 ± 3.22	48.51 ± 6.80	47.28 ± 4.20
Neutrophils p/n, %	2.70 ± 0.31	2.52 ± 0.41	2.33 ± 0.42
Eosenophils,%	2.29 ± 0.31	1.52 ± 0.41*	2.0 ± 0.68
Platelets, 10^6/ml	379.67 ± 25.70	427.50 ± 91.56#	407.52 ± 47.04#
Platelet, %	0.13 ± 0.03	0.24 ± 0.04*	0.21 ± 0.02*
Fraction of large platelets, %	41.83 ± 5.14	65.23 ± 8.58*	61.50 ± 8.65*

*Notes. In this and other tables in this section: *we marked a significant difference ($p < 0.05$) of parameters in experimental groups in comparison with those in control group of animals; #we marked tendency to changes ($p < 0.1$).*

increase of prothrombin index (23.6 %) and insignificant decrease of PTC index (by 11.0 %) (Table 2).

Fibrinogen is known to be blood-clotting factor I, produced in the liver. Through the action of active plasma enzymes, it is converted into fibrin, which is involved in the formation of a blood clot and thrombus. The plasma fibrinogen content is an important diagnostic marker of thrombosis and inflammation, directly linked to cardiovascular disease. Fibrinogen is also an acute phase protein, and its concentration in the blood increases in diseases accompanied by tissue damage and

Table 2

Changes of peripheral blood coagulometric indices in rats after a single intratracheal administration of colloidal solutions of Fe_2O_3 with 19 nm and 400 nm particles (M ± m, n = 10)

Indexes	Groups of Animals		
	Control	Fe_2O_3 19 nm	Fe_2O_3 400 nm
Fibrinogen, mg/dl	258.4 ± 8.7	744.4 ± 56.4*	709.4 ± 37.8*
Prothrombintime, s	18.3 ± 1.3	15.9 ± 0.3	16.3 ± 0.4
Prothrombinindex, %	55.3 ± 1.2	57.8 ± 1.5	68.4 ± 3.8*
Activated partial thrombo-plastin time (APTT), s	19.9 ± 1.2	19.5 ± 0.3	17.7 ± 0.8
Thrombintime, s	14.2 ± 2.4	7.9 ± 0.2*	7.4 ± 0.2*

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inflammation. The determination of fibrinogen levels in the coagulogram is important in the diagnosis of diseases with increased bleeding or thrombosis, as well as in the assessment of liver synthetic function and risk of cardiovascular complications [14].

Consequently, the elevated levels of fibrinogen in the blood of experimental rats injected with colloidal solutions of Fe_2O_3 may indicate their effect on the final stage of blood clotting (formation of fibrin from fibrinogen), as well as on the development of the inflammatory process.

Increased prothrombin index, especially after administration of Fe_2O_3 400 nm (1.3 times) may indicate the activation of thrombus. The thrombin time index was halved upon exposure to both Fe_2O_3 solutions (Table 2).

Consequently, the increased levels of fibrinogen in the blood of experimental rats, which were administered colloidal solutions of Fe_2O_3, may indicate increased thrombus formation and risk of cardiovascular complications, as well as the presence of an inflammatory process. Increased thrombus formation may be indicated by a decrease in INR and an increase in the prothrombin index (PTI) determined after administration of Fe_2O_3 400 nm.

The simulation of subchronic intoxication in experimental rats injected with Fe_2O_3 19 nm revealed a significant increase (2.0 times) in the level of zincprotoporphyrin (ZPP), a slight decrease in the number of red blood cells and hemoglobin concentration (by 10.0 %) and haematocrit (by 11.0 %). After 30 injections of iron oxide solution with 400 nm particles, the number of erythrocytes, hemoglobin and hematoglobin levels were reduced (by 18.2 %; 8.0 % and 4.0 % compared with controls) (Table 3).

In the 1st experimental group of rats, after 30 injections of Fe_2O_3 19 nm, there was a significant decrease in white blood cell and eosinophils counts (by 52.0 % and 34.0 %, $p < 0.05$ compared with the control group of animals). The

Table 3

Peripheral blood parameters of control and experimental rats after 30 injections of Fe_2O_3 colloidal solutions with 19 nm and 400 nm particles (M ± m, n = 10)

Indexes	Groups of animals		
	Control	Fe_2O_3 19 nm	Fe_2O_3 400 nm
CPP, mM/M heme	70.75 ± 4.38	135.63 ± 2.58*	70.75 ± 4.38
Hemoglobin, g/l	157.10 ± 2.80	141.50 ± 0.19#	145.10 ± 1.50#
Erythrocytes, 10^9/ml	9.25 ± 0.33	8.18 ± 0.09#	7.61 ± 0.28*
Hematocrit, %	49.27 ± 0.97	44.22 ± 0.55#	47.59 ± 0.75
Leukocytes, 10^6/ml	11.88 ± 0.99	5.74 ± 0.38*	11.77 ± 0.94
Lymphocytes, %	61.05 ± 3.83	65.81 ± 3.06	62.87 ± 3.83
Monocytes, %	5.87 ± 0.33	4.73 ± 0.40	7.93 ± 0.57*
Neutrophils s/n, %	26.89 ± 4.01	22.59 ± 1.15	32.52 ± 1.64*
Neutrophils p/n, %	2.70 ± 0.31	2.52 ± 0.41	2.33 ± 0.42
Eosenophils, %	2.29 ± 0.31	1.52 ± 0.41*	2.0 ± 0.68
Platelets, 10^6/ml	586.6 ± 19.9	653.6 ± 12.9	889.6 ± 22.4*
Platelet, %	0.49 ± 0.04	0.61 ± 0.03*	0.72 ± 0.04*

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number of lymphocytes, monocytes and neutrophils in the blood of the experimental rats of this group did not differ significantly from the control values. After administration of colloidal Fe_2O_3 solution with 400 nm particles there was detected a significant increase in the number of monocytes and segmented neutrophils (by 35.1 % and 21.0 %, $p < 0.05$ in comparison with the control group of animals) (Table 3). Such changes in the cellular composition of the blood may indicate the activation of the cells of nonspecific natural immunity and the formation of an inflammatory reaction.

The investigation of coagulation system indices showed, that in both experimental groups of rats in comparison with the control group there was increased number of thrombocytes (by 11.4 % and 51.6 %), as well as thrombocrit (by 24.5 % and 46.9 %) ($p < 0,05$).

It is known that in addition to platelets in the cascade of biochemical reactions, which results in the formation of fibrin clot, participate plasma components (clotting factors).

The results of the study showed that after 30-fold injection of colloidal solutions of iron oxide Fe_2O_3 (particle size 19 nm and 400 nm) to the experemental rats, significant changes in the coagulogram parameters were observed in comparison with the control group of animals. It should be noted, that both in the 1st and in the 2nd experimental groups, there was an increase of the fibrinogen level (by 23.0 % and 8.3 %, correspondingly), a decrease of the prothrombin index (by 46.2 % and 12.2 %) and a decrease of the thrombin time (by 26.7 % and 56.3 % ($p < 0,05$) (Table 4).

Thus, our data correlate with the sources [4, 15] and indicate that Fe_2O_3 nanoparticles, when administered to rats for a prolonged period of 30 times, affected both cellular (increased platelet count) and humoral components of the clotting system (increased fibrinogen level, thrombin time), indicating hypercoagulative properties of iron oxide nanoparticles and an increased risk of thrombus formation.

After processing the primary data obtained during the experiments and analyzing the results of each of the models studied, a comparative analysis of changes in peripheral blood values relative to those in the control groups was performed for each model, taking into account the particle size in Fe_2O_3 colloidal solutions (Figure 1). This analysis makes it possible to identify the most significant changes in individual blood parameters for each model and assess the degree of toxic effects depending on particle size, dose received and time of their exposure to the body.

Table 4

Changes of peripheral blood coagulometric indices in rats after 30 injections of colloidal Fe_2O_3 solutions with 19 nm and 400 nm particles (M ± m, n = 10)

Indexes	Groups of animals		
	Control	Fe_2O_3 19 nm	Fe_2O_3 400 nm
Fibrinogen, mg/dl	240.0 ± 6.1	295.4 ± 5.0*	260.0 ± 6.0
Prothrombintime, s	18.0 ± 1.3	16.5 ± 0.3	15.5 ± 0.4
Prothrombinindex,%	87.2 ± 2.4	47.0 ± 1.6*	76.6 ± 1.3*
Activated partial thrombo-plastin time (APTT), s	20.2 ± 1.2	17.5 ± 0.3	16.7 ± 0.6
Thrombintime, s	60.0 ± 0.7	44.0 ± 1.0*	26.2 ± 0.4*

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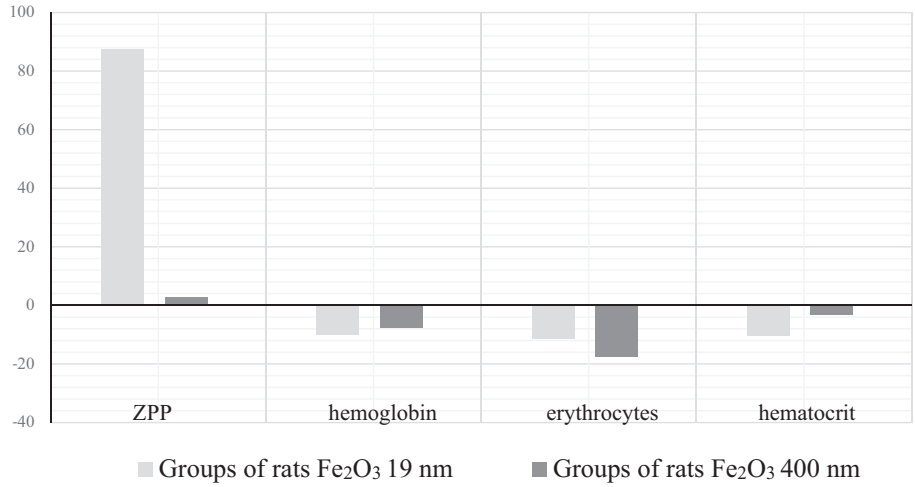

Figure 1. Changes of peripheral blood parameters relative to control groups in % for each model taking into account the particle size in Fe_2O_3 colloidal solutions

Comparison of changes in control parameters showed that for both models the content of zincprotoporphyrin, total concentration of hemoglobin and number of erythrocytes in the blood are significant indicators. The results indicate significant disturbances in the processes of hematopoiesis. In both models, anemia developed in rats of all experimental groups, although due to a different mechanism of action of nanoparticles. Thus, the sharp decrease in the number of erythrocytes in the animals injected with colloidal Fe_2O_3 400 nm can be attributed not so much to their cytotoxic effect as to the disruption of the hematopoiesis process (Figure 1).

The investigation revealed a significant decrease in the total number of leucocytes under intoxication with NPs Fe_2O_3 19 nm and an increase in the proportion of monocytes in the leucocytic formula under the action of Fe_2O_3 400 nm, which may indicate activation of macrophage-monocytic cells aimed at elimination of foreign agents (Figure 2).

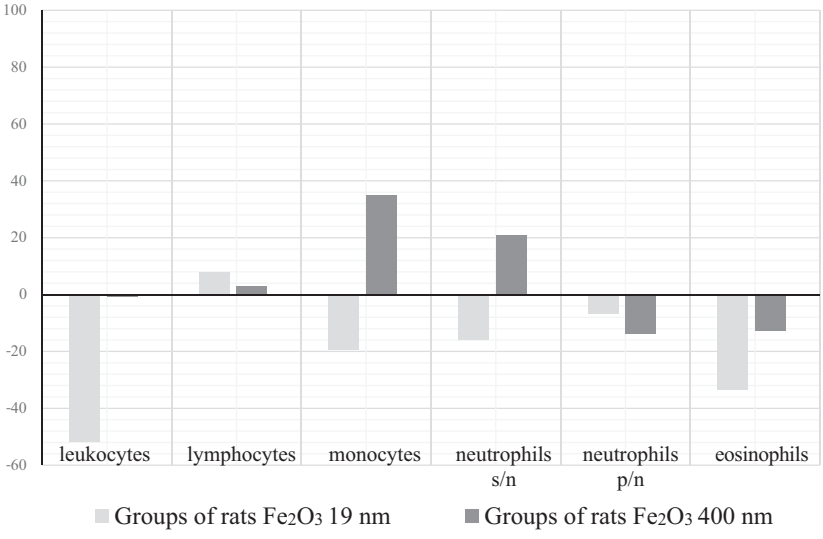

Figure 2. Changes in peripheral blood counts (leukocyte counts) relative to control groups in % for each model, taking into account the particle size in Fe_2O_3 colloidal solutions

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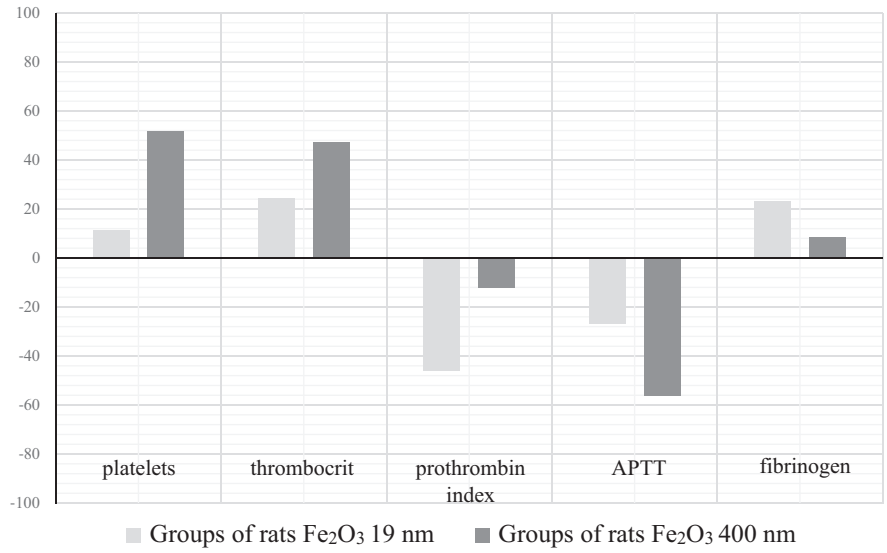

Figure 3. Comparative analysis of changes in blood coagulation indices relative to control groups in % for each model taking into account particle size in Fe_2O_3 colloidal solutions

When modeling acute intoxication with intratracheal administration of Fe_2O_3 solutions, an increase of thrombocrit against the background of a relatively small change in platelet count was fixed, while during subchronic intoxication with Fe_2O_3 400 nm an increase both in thrombocrit and platelet count was fixed. Also in acute intoxication was fixed more fibrinogen than in subchronic, which is a sign of a greater risk of thrombosis in the first case, but at the same time, a significant decrease in activated partial thromboplastin time, correlated with an increase in platelet count, in subchronic Fe_2O_3 intoxication indicates a high risk of thrombus formation due to decreased blood viscosity (Figure 3).

Significant changes in the indices characterizing the state of platelet cells and coagulogram indicate serious disturbances in the blood coagulation system and the maintenance of its aggregate state.

Thus, the obtained results of investigation of changes in the peripheral blood and coagulometric indexes under the action of colloid solutions of Fe_2O_3 with the particles of different dispersion make it possible to draw the following conclusions.

Conclusions

1. Single intratracheal injection of Fe_2O_3 colloid solutions caused changes of hematological parameters (increase of zincprotoporphyrin level and decrease of hemoglobin, decrease of erythrocyte and platelets amount, hematocrit, leukocyte amount, increase of monocytes) which indicates a violation of hematopoiesis and the process of hemoglobin synthesis.
2. Prolonged intoxication of fine particles Fe_2O_3 colloid solutions caused a significant decrease of the total number of erythrocytes and leukocytes, which, together with disruption of the process of hemoglobin synthesis, may indicate the development of anemia.
3. Both acute and chronic Fe_2O_3 colloid solutions intoxication in rats resulted in changes of parameters characterizing the state of platelet cells and coagulogram, indicating serious disturbances in the blood coagulation system, a high risk of thrombus formation due to decreased blood viscosity. This assumption requires further expansion of toxicological studies on the safety of artificially synthesized Fe_2O_3 medical nanoparticles for human health.

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