

Research Article**Physiological response of the hemostatic system in newborn calves with iron deficiency to the use of ferroglucin and glycopin**

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[Received: 15/02/2019; Accepted: 10/04/2019; Published: 12/04/2019]

ABSTRACT

Objective: to establish the effect of a combination of ferroglucin and glycopine on the functional activity of the hemostasis system in newborn calves with iron deficiency anemia.

Material and methods: The work was performed on 45 newborn calves with iron deficiency anemia, having erythropoiesis disorders and signs of a decrease in the level of iron in their bodies. The control consisted of 29 healthy newborn calves. For the correction of iron deficiency in all 45 observed newborn calves, use of ferroglucin was carried out at 75 mg (1 ml) intramuscularly, once, at the rate of 15 mg of iron per 1 kg of body weight and feeding of glycopine at 6 mg/day in the morning in a combination of 6 days, starting simultaneously with injection ferroglucin. Used biochemical, hematological and statistical research methods.

Results: In modern conditions of great scientific and practical importance is the search for options for the effective correction of hemostasiopathy in case of iron deficiency. Of great interest is the correction potential for hemostasis disorders as a powerful stimulator of the growing body glycopine in combination with an iron-containing agent in newborn calves with iron deficiency. During the examination of 45 newborn calves with iron deficiency anemia, a decrease in the antioxidant protection of blood plasma with the intensification of lipid peroxidation processes in it was established. In these animals, an increase in the hemostatic activity of platelets and the blood coagulation system is noted, with the suppression of the ability of the vascular wall to limit the activity of these components of hemostasis. The use of ferroglucin and glycopine in newborn calves with iron deficiency anemia normalized the antioxidant protection of blood plasma, the processes of lipid peroxidation in it, and also completely normalized the platelet, vascular and plasma components of the hemostatic system.

Conclusion: It was found out that for newborn calves with an iron deficiency, an increase in the hemostatic abilities of platelets and plasma hemostasis is observed with a weakening of vascular control, forming hemostasiopathy, which can be completely eliminated using a combination of ferroglucin and glycopine.

Keywords: Iron deficiency, Newborn calves, Hemostatic system, Ferroglucin, Glycopin.

INTRODUCTION

Currently, iron deficiency anemia in newborn calves is still often found in many livestock farms in Russia, negatively affecting the growth and development of animals, weakening their resistance to environmental factors and often causing their death.¹ It was noted that in various

negative states of the body, including those with micronutrient deficiencies, hemostasis activity may increase, which leads to the formation of obvious thrombophilia.^{2,3}

The fairly widespread prevalence of iron deficiency anemia in newborn calves causes a

high incidence of violations in the hemostasis system as a whole.⁴ However, these changes are still insufficiently investigated. In addition, in modern conditions, the possibilities of correcting hemostasiopathy in the iron deficient state are not fully clarified. The effect on hemostasis of one of the modern powerful stimulants of the vital activity and resistance of a growing organism, glycopine (glucosaminylmuramyl dipeptide), remains unknown. He showed efficacy as a stimulator of immune responses and metabolic processes in a number of negative states.⁵ At the same time, the effect of this drug in combination with an iron-containing agent on newborn calves with an iron deficiency dysfunction in the hemostasis system is not assessed.

In this regard, in this paper, the goal is to establish the effect of a combination of ferroglucin and glycopine on the functional activity of the hemostasis system in newborn calves with iron deficiency anemia.

MATERIALS AND METHODS

Research was conducted in strict accordance with ethical principles established by the European Convent on protection of the vertebrata used for experimental and other scientific purposes (adopted in Strasbourg March 18, 1986, and confirmed in Strasbourg June 15, 2006).

The work was performed on 45 newborn calves with iron deficiency anemia, with erythropoiesis disorders and signs of a decrease in the level of iron in their body (serum iron $12.6 \pm 0.17 \mu\text{mol/l}$, siderocytes $1.7 \pm 0.08\%$, hemoglobin $96.1 \pm 0.24 \text{ g/l}$, erythrocytes $4.3 \pm 0.24 \times 10^{12}/\text{l}$). The control consisted of 29 healthy newborn calves.

The severity of lipid peroxidation (LPO) of plasma was assessed by the concentration of thiobarbituric acid-active products using the Agat-Med kit (Russia) and acylhydroperoxides, taking into account the antioxidant potential of the liquid blood.⁶ The concentration of platelets in the blood was determined using the camera Goryaeva. The state of platelet aggregation (AP) was detected by a visual micromethod with a number of inductors: ADP ($0.5 \times 10^{-4} \text{ M}$), collagen (dilution 1:2 of the main suspension),

thrombin (0.125 units/ml), ristomycin (0.8 mg/ml), adrenaline ($5 \times 10^{-6} \text{ M}$) with a standardized number of platelets in the plasma studied 200×10^9 platelets. Intravascular platelet activity was determined by phase-contrast microscopy.

Anti-aggregation activity of the vessel wall was found in a sample with temporary venous occlusion⁷ based on a visual micro-method of AP registration with all inductors used and their combinations by calculating the anti-aggregation index of the vascular wall by dividing the AP time against the background of venous congestion by the time when AP appeared without it. The index of the anticoagulant activity of the vessel wall in the observed calves was determined by dividing the activity of antithrombin III after venous occlusion by its value before it.⁷ The state of vascular control of blood fibrinolytic activity was determined by recording the time of euglobulinolysis before and after temporary venous occlusion⁷ by calculating the index of fibrinolytic activity of the vascular wall by dividing the time of euglobulinolysis before occlusion by the time of lysis after it.

To assess the coagulation ability of blood plasma in each calf taken under observation, the duration of the activated partial thromboplastin time, prothrombin and thrombin time was determined.⁷ For the correction of iron deficiency in all 45 observed newborn calves, use of ferroglucin was carried out at 75 mg (1 ml) intramuscularly, once, at the rate of 15 mg of iron per 1 kg of body weight and feeding of glycopine at 6 mg/day in the morning in a combination of 6 days, starting simultaneously with injection ferroglucin. Statistical processing of the data was carried out by t-student criterion.

RESULTS

In newborn calves with an iron deficiency, disturbances in the general condition of animals characteristic of anemia were revealed: weakness, lethargy, lack of interest in the surroundings, pallor of the nasal mirror and visible mucous membranes.

In animals with iron deficiency, a high activity of free radical oxidation of lipids in the liquid

part of the blood was noted (acylhydroperoxide 3.38 ± 0.17 D₂₃₃/1 ml, thiobarbituric acid-active products 5.16 ± 0.31 $\mu\text{mol/l}$ with an antioxidant activity of $22.4 \pm 0.19\%$). Analogous values in the control were 1.44 ± 0.09 D₂₃₃/1 ml, 3.46 ± 0.14 $\mu\text{mol/l}$ and $33.7 \pm 0.14\%$, respectively.

The content of platelets in the blood of newborn calves with anemia corresponded to the norm.

At the same time, AP in the observed animals with anemia was accelerated. AP occurred most early under the action of collagen (19.6 ± 0.17 s), somewhat later in response to ADP and ristomycin, and even later with thrombin (37.0 ± 0.09 s). The most delayed in calves with iron deficiency in AP came under the influence of adrenaline (69.7 ± 0.10 s) (table).

Table. Hemostasis in newborn calves with iron deficiency treated with ferroglucin and glycopin

Registered indicators	Ferroglucin and glycopene, n=45, M \pm m		Control, n=29, M \pm m
	exodus	after correction	
Aggregation with ADP, s	25.2 \pm 0.12	40.0 \pm 0.06 p ₁ <0.01	40.2 \pm 0.08 p<0.01
Aggregation with collagen, s	19.6 \pm 0.17	31.2 \pm 0.05 p ₁ <0.01	31.4 \pm 0.08 p<0.01
Aggregation with thrombin, s	37.0 \pm 0.09	54.0 \pm 0.14 p ₁ <0.01	53.8 \pm 0.07 p<0.01
Aggregation with ristomycin, s	22.6 \pm 0.18	47.9 \pm 0.08 p ₁ <0.01	48.0 \pm 0.12 p<0.01
Aggregation with adrenaline, s	69.7 \pm 0.10	97.8 \pm 0.05 p ₁ <0.01	97.6 \pm 0.06 p<0.01
Discocytes, %	58.6 \pm 0.26	78.3 \pm 0.10 p ₁ <0.01	77.7 \pm 0.11 p<0.01
Sum of active forms, %	41.4 \pm 0.25	21.7 \pm 0.09 p ₁ <0.01	22.3 \pm 0.11 p<0.01
The number of small units of 2-3 platelets per 100 free-lying platelets	14.5 \pm 0.09	3.7 \pm 0.12 p ₁ <0.01	3.5 \pm 0.06 p<0.01
The number of medium and large units, 4 or more platelets per 100 free-lying platelets	3.18 \pm 0.23	0.12 \pm 0.003 p ₁ <0.01	0.14 \pm 0.007 p<0.01
The index of antiaggregatory activity of the vascular wall with ADP	1.45 \pm 0.06	1.67 \pm 0.08 p ₁ <0.01	1.67 \pm 0.12 p<0.01
The index of antiaggregatory activity of the vascular wall with collagen	1.36 \pm 0.12	1.56 \pm 0.09 p ₁ <0.01	1.58 \pm 0.02 p<0.01
The index of antiaggregatory activity of the vascular wall with thrombin	1.39 \pm 0.11	1.52 \pm 0.02 p ₁ <0.01	1.52 \pm 0.05 p<0.01
Index antiaggregatory activity of the vascular wall with ristomycin	1.46 \pm 0.11	1.51 \pm 0.05 p ₁ <0.01	1.51 \pm 0.04 p<0.05
The index of antiaggregatory activity of the vascular wall with adrenaline	1.41 \pm 0.07	1.65 \pm 0.05 p ₁ <0.01	1.64 \pm 0.07 p<0.01
Activity antithrombin III, %	83.9 \pm 0.23	99.7 \pm 0.16 p ₁ <0.01	99.3 \pm 0.16 p<0.01
Activity antithrombin III activity after temporary venous occlusion, %	104.9 \pm 0.16	130.6 \pm 0.16 p ₁ <0.01	130.5 \pm 0.06 p<0.01
The index of anticoagulant activity of the vascular wall	1.25 \pm 0.05	1.31 \pm 0.04 p ₁ <0.01	1.31 \pm 0.03 p<0.01
Spontaneous time euglobulinolysis, minutes	239.2 \pm 0.26	182.6 \pm 0.39 p ₁ <0.01	182.0 \pm 0.39 p<0.01
Spontaneous time euglobulinolysis after temporary venous occlusion	296.3 \pm 0.19	253.0 \pm 0.05 p ₁ <0.01	252.6 \pm 0.50 p<0.01
Fibrinolytic index vascular wall activity	1.24 \pm 0.08	1.38 \pm 0.03 p ₁ <0.01	1.39 \pm 0.10 p<0.01
Activated partial thromboplastin time, s	28.2 \pm 0.38	39.4 \pm 0.42 p ₁ <0.01	39.7 \pm 0.34 p<0.01
Prothrombin time, s	12.4 \pm 0.24	17.2 \pm 0.36 p ₁ <0.01	17.4 \pm 0.23 p<0.01

Thrombin time, s	16.0±0.15	17.1±0.19 p ₁ <0.01	17.2±0.21 p<0.01
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Legend: p - reliability of differences in indicators between the control and the initial state of calves, p₁ - reliability of the dynamics of the indicators taken into account in the background of the correction. In the following tables, the designations are similar.

In the blood of anemized calves, the quantitative content of discoid platelets reached 58.6±0.26%. In this case, the sum of the active forms of platelets in them was 41.4±0.25%. Small and large aggregates in the bloodstream of sick animals contained - 14.5±0.09 and 3.18±0.23 per 100 free-lying platelets, respectively (table).

In anemized animals included in the study, a decrease in the index of antiaggregatory activity of the vascular wall was observed with all inducers and their combinations used (table). The lowest was the index of antiaggregatory activity of the vascular wall with collagen. A slightly higher level of the index of antiaggregatory activity of the vascular wall was registered with adrenaline and thrombin. They were superior to the antiaggregation index of the vascular wall with ADP (1.45±0.06) and ristomycin (1.46±0.11).

The observed newborn calves with anemia showed a weakening of the anticoagulant capabilities of the vascular wall, estimated by the value of the antiaggregation index of the vascular wall.

The severity of the fibrinolytic activity of blood vessels in anemized newborn calves, associated with the production of plasminogen activators in the vascular wall and recorded for the duration of euglobulinolysis before and after the test with metered venous occlusion, was significantly weakened (vascular wall fibrinolytic activity index was 10.8%).

For calves with iron deficiency, acceleration of clotting time along the external pathway (prothrombin time 12.4±0.24 s), internal pathway (activated partial thromboplastin time 28.2±0.38 s) and intensification of fibrinogen to fibrin transition (thrombin time 16.0±0.15 s).

The correction provided normalized general condition, level of iron and hematological parameters taken into account in anemic calves.

Against the background of ferroglycin and glycopine, it was possible to normalize the content in the plasma of acyl hydroperoxide (1.45±0.18 D₂₃₃/1 ml), thiobarbituric acid-active products (3.43±0.21 μmol/l) and the magnitude of antioxidant activity (33.5±0.11%).

As a result of correction in animals with anemia, inhibition of antibodies to the level of control was observed. At the same time, against the background of the correction, the platelets of the animals reacted most actively to collagen, ADP and ristomycin, less actively to thrombin and adrenaline (table).

The applied correction caused the complete normalization of the intravascular platelet activity in the observed newborn calves with iron deficiency (table). The number of discocytes in the bloodstream of these animals increased to 78.3±0.10% with a decrease in the total value of the active forms of blood plates to 21.7±0.09%. This led to a reduction in the blood of animals to the level of control of the number of freely circulating aggregates of various sizes.

In anemized animals that received correction, an increase to the level of the norm of the antiaggregatory activity index of the vascular wall was observed with all inducers used (table). The lowest index was the antiaggregatory activity of the vascular wall with collagen. A slightly higher level of the index of antiaggregatory activity of the vascular wall was registered with adrenaline and thrombin. They were superior to the indexes of antiaggregatory activity of the vascular wall with ADP (1.67±0.08) and ristomycin (1.51±0.05).

In newborn calves with anemia that received correction, normalization of vascular wall anticoagulant activity was noted.

The application of the correction ensured the normalization of the effects of the vascular wall on the fibrinolytic ability of blood in anemic newborn calves. This was indicated by the normalization of the duration of euglobulinolysis

before and after the test with metered venous occlusion and the value of the index of fibrinolytic activity of the vascular wall.

By the end of the correction in calves, time normalization in coagulation tests was noted (table). Thus, as a result of the exposure, inhibition of the antiaggregatory activity index of the vascular wall was achieved by 39.7% with a simultaneous slowing down of the prothrombin time by 38.7%. At the same time, the thrombin time, which determines the intensity of the transition of fibrinogen to fibrin, in calves receiving ferroglucin and glycopin, increased by 6.9%, also reaching a control level.

DISCUSSION

The development of various dysfunctions in the body is always accompanied by impaired functioning of many organs and systems in it^{8,9}, including the hemostasis system^{10,11}. The weakening of the antioxidant protection of the plasma of newborn calves with anemia against the background of hypoxia arising in them was accompanied by the activation of PLO in their plasma. This damaged the structure of blood corpuscles in them¹², including platelets and blood vessels¹³, causing the violation of their functions.^{14,15} The increase in newborn calves with anemia of antibodies to individual inductors in vitro indicates an increase in their sensitivity to stimulating effects.¹⁶ An increase in AP with ristomycin in calves with anemia indicates an increase in their sensitivity to von Willebrand factor.^{17,18} Acceleration of AP with ADP in these animals indirectly indicates an increase in the intensity of arachidonic acid metabolism in their blood plates with an increase in the generation of a powerful platelet aggregation stimulator, thromboxane, in them.¹⁹ The found acceleration of antibodies with combinations of aggregation inducers in newborn calves with anemia largely reflected in them an increase in the interaction of platelets in conditions close to in vivo.²⁰ High intravascular activity of platelets in anemic animals confirmed the intensification of the aggregation process of blood plates in the bloodstream, undoubtedly being associated with pronounced alteration of endotheliocytes, leading to significant

accessibility to their subendothelial structures.^{21,22}

The decrease in the newborn calves with anemia of the antiaggregatory activity of the vascular wall was confirmed on the model with the combined use of aggregation inducers, showing the insufficiency of the production of vascular disaggregating substances, in conditions substantially close to the real blood flow, in which a number of agonists are simultaneously present.²³

A prominent role in the occurrence of vasopathy with the lack of atrombogenic activity of the vascular wall in anemized calves in the neonatal phase belongs to the weakening of its anticoagulant and fibrinolytic properties.²⁴ The revealed negative dynamics of the anticoagulant capacity of the vessels is caused by a decrease in the production of antithrombin-III, one of the most powerful physiological anticoagulants in animals in the intact endothelium.²⁵ A marked decrease in the control of the vascular wall of newborn calves with anemia over the fibrinolytic activity of their blood was based on depression of the intensity of synthesis in the endothelium of tissue plasminogen activators.²⁶ Acceleration of prothrombin time in these animals reflected the intensification of the mechanisms of plasma hemostasis activation along the external path and was largely due to the increased formation of highly active thromboplastin in them.^{27,28} The rapidity of the activated partial thromboplastin time reflected an increase in the functioning of the internal coagulation path with an acceleration of the final stage of hemocoagulation, assessed by the thrombin time.²⁹

The use of ferroglucin and glycopine caused in the newborn calves the saturation of their body with iron with the restoration of the indicators of red blood and the general condition of the animals.

The combined use of ferroglucin and glycopine significantly reduced in calves with iron deficiency the intensity of the PLO process in the liquid part of the blood, weakening its stimulating effect on the surface structure of platelets. Inhibition of AP and a decrease in intravascular platelet activity in calves with iron

deficiency anemia as a result of the use of ferroglucin and glycopine is largely a consequence of the positive impact of the correction on the intensity of lipid peroxidation, receptor and postreceptor mechanisms of platelet functioning.^{30,31} Lengthening the time of occurrence of AP under the action of ristomycin indicated a decrease in the blood of calves fed ferroglucin and glycopin, von Willebrand factor.

Intensification of LPO in plasma in newborn calves with anemia lowered the antiaggregation ability of the vessel wall, apparently as a result largely due to the weakening of the synthesis of prostacyclin and NO in it, adversely affecting the microcirculation process in tissues.³² Thus, the temporary ischemia of the venous wall in these animals revealed a weakening of vascular control over the adhesive ability of the blood plates. It was realized, at a minimum, through insufficiency of vascular control over the density of collagen receptor glycoproteins Ia-IIa and VI on the platelet membrane, judging by the non-expression of inhibition of AP with collagen against the background of temporary venous ischemia³³, as well as a result of a significant increase in von Willebrand factor production in the structures of blood vessels with an increase in the number of receptors to it - (GPIb) on the surface of the blood platelets with the insufficiency of the limiting influence on this process of the level of production in the vessels of physiological antia regantov.^{34,35}

At the same time, against the background of low release of antiplatelet vessels, excessive fixation of strong aggregation agonists – collagen and thrombin to their receptors on the platelet membrane – is possible, which inevitably enhances the phospholipase C activity in them. systems.³⁶ Under conditions of lack of education in the vessels of PGI₂ and NO, excessive activity of influencing the platelets of weak aggregation inducers - ADP and adrenaline is also possible, accompanied by excessive expression of fibrinogen receptors (GPIIb-IIIa) and significant activity of phospholipase A₂, regulating the release of platelet phospholipids arachidone) .

As a result of the applied effect, it was possible to normalize the anticoagulant and fibrinolytic abilities of the vascular wall in the newborn

anemized calves. This consisted in enhancing the production of antithrombin-III in the endothelium of these animals with an increase to the level of production of tissue plasminogen activators in it.

At the same time, in newborn calves, which received ferroglucin and glycopine, normalization of metabolic and synthetic processes in the liver, characteristic of iron deficiency, occurred. A gradual slowdown to the level of prothrombin control reflected the normalization of the mechanisms of plasma hemostasis activation along the external pathway and was largely due to the normalization of the intensity of formation and activity that triggers the clotting of thromboplastin.³⁸

The inhibition on the background of the correction to the control level of the initially accelerated activated partial thromboplastin time reflected a decrease in the activity of the internal coagulation path during deceleration of the final stage of hemocoagulation, assessed by thrombin time.³⁹ The achieved dynamics of plasma coagulation activity provides calves receiving correction with the optimal level of blood liquid properties for their development and optimal perfusion of internal organs, supporting the necessary metabolic rate for its further growth and development in calf tissues.⁴⁰

CONCLUSION

Iron deficiency in newborn calves is still common in many livestock farms in Russia. It negatively affects the growth and development of animals, weakens their resistance to environmental factors and often causes their death. It is noted that in various deficient states in the body of young animals it is possible to increase the activity of hemostasis and the formation of thrombophilia. It was found that for newborn calves with iron deficiency anemia, it is characteristic of a decrease in the antioxidant protection of blood plasma and an intensification of lipid peroxidation processes in it. In conditions of iron deficiency anemia in newborn calves, an increase in the hemostatic activity of platelets and the blood coagulation system is noted while suppressing the ability of

the vascular wall to restrict this process. In newborn calves with iron deficiency anemia, receiving ferroglucin and glycopin, rapid normalization of the antioxidant protection of blood plasma and lipid peroxidation processes in it is noted. In the case of the use of ferroglucin and glycopine in newborn calves with iron deficiency anemia, full normalization of the platelet, vascular and plasma components of the hemostasis system is possible.

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