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Functional Features Of Primary Hemostasis In Newborns Calves With Functional Disorders Of The Digestive System.

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ABSTRACT

It is known that it is the increased platelet activity that often plays a major role in the activation of hemostasis in general, increase in viscosity and deterioration of the blood microcirculation with an increased risk of intravascular thrombosis. Disturbances of platelet aggregation, antiaggregatory activity of the vascular wall and the intravascular activity of the platelets in newborn calves with functional disorders of digestion remain understudied. In the work carried out in newborn calves with functional digestive disorders, an increase in platelet aggregation function in vitro and in vivo was detected. These disorders are based on deep changes in the lipid composition of platelet membranes, an increase in the level of medium molecules in plasma and blood plates, activation of lipid peroxidation in them, increased synthesis in the vascular wall of von Willebrand factor and intensification of thromboxane formation in blood plates. Activation of thromboplastin formation can be considered the leading cause of increased blood coagulation in newborn calves with functional digestive disorders. On the basis of the studies performed, it can be said that the correction of violations of the platelet hemostasis should include a pathogenetically determined complex capable of simultaneously leveling functional disorders of the digestive system and optimizing blood rheology simultaneously.

Keywords: platelets, newborn calves, functional disorders of the digestive system.

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INTRODUCTION

The study of dysfunctions of primary hemostasis in newborn calves with functional disorders of the digestive system is of great scientific and practical importance [1,2] due to the fact that it is the increased platelet activity that plays a major role in the activation of hemostasis in general [3-6], increase in viscosity [7 , 8] and deterioration of microcirculation of blood [9,10] with an increased risk of intravascular thrombus formation [11,12]. At the same time, violations of platelet aggregation, anti-aggregation activity of the vascular wall and the intravascular activity of platelets in newborn calves with functional disorders of digestion are not well understood. No abnormalities have been identified in newborn calves with functional disorders of the digestion of the lipid composition of their membranes, the level of peroxidation and antioxidant protection of platelets, and the exchange of arachidonic acid in them. In the available literature there are fragmentary information that functional disorders of the digestive system are accompanied in newborn calves by an increase in the plasma content of medium molecules [13], which can adversely affect many functions of the body. The level of medium molecules in platelets, to which their content in newborn calves with functional digestive disorders increases, has not been evaluated, contributing in many ways to the development of platelet dysfunctions [14].

The purpose of the work is to find out the peculiarities of the violation of primary hemostasis in newborn calves with functional digestive disorders.

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) and approved by the local ethic committee of Russian State Social University (Record №12 dated December 3, 2015).

The study included 153 newborn calves with functional digestive disorders for a period of 1-3 days from healthy cows 1-2 calves. Animal feeding and maintenance was carried out in standard calf conditions. The control group is represented by 267 healthy newborn calves. Blood sampling from animals was carried out in the morning. The following indicators were determined. The content of medium molecules in plasma and washed and resuspended platelets was evaluated. The level of lipid peroxidation (LPO) plasma was detected on the content of thiobarbituric acid-reactive substances set of the company "Agate-Med" atsilgidroperekisey (AHP), and the activity Thrombocyte lipid content basal level of malondialdehyde (MDA) in the reduction reaction of thiobarbituric acid and AHP. The intra-platelet antioxidant system of platelets was evaluated by the activity of catalase and superoxide dismutase.

In the washed and resuspended platelets, the cholesterol content was determined by an enzymatic colorimetric method using Vital Diagnosticum and phospholipids using phosphorus. The activity and time of formation of endogenous thromboplastin were evaluated. An indirect assessment of the level of arachidonic acid exchange in platelets and its transformation enzymes - cyclooxygenase and thromboxane synthetase was performed using 3 transfer tests with registration of platelet aggregation (AP) on a photoelectrocolorimeter. The number of platelets in the capillary blood in the Goryaev chamber was counted. The platelet aggregation ability was studied by a visual micromethod with ADP inductors (0.5×10^{-4} M), collagen (dilution 1: 2 of the main suspension), thrombin (0.125 units / ml.), ristomycin (0.8 mg/ml), adrenaline (5×10^{-6} M). In order to simulate the real conditions of the blood flow, combinations of inductors ADP + adrenaline, ADP + collagen and adrenaline + collagen in the same concentrations were used. Morphologically, the intravascular activity of platelets was assessed using a phase-contrast microscope. The state of antiaggregation activity of the vessel wall with all inductors used was evaluated against the background of temporary venous occlusion with the calculation of the index of antiaggregatory activity of the vascular wall (IAAVW). Processing of the results obtained was carried out using Student's t-test.

RESULTS

In newborn calves with functional digestive disorders, an increase in plasma LPO activity was detected. At the same time, the concentration of thiobarbituric acid -active products in plasma was at the level of 5.10±0.02 µmol/l, in the control - 3.92±0.06 µmol/l. The content of MDA in platelets was also increased

(1.54±0.004 nmol/10^9 platelets) versus control (0.89±0.02 nmol/10^9 platelets), indicating the activation of free-radical oxidation in them due to the weakening of intra-platelet antioxidant activity. The amount of AHP in the plasma of sick calves reached 3.50±0.01 D_{233}/1 ml (in the control 1.92±0.02 D_{233}/1 ml) In the blood plates of patients with AHP (3.49±0.01 D_{233}/10^9 platelets) also significantly exceeded the control values (2.87±0.04 D_{233}/10^9 platelets).

Increased free-radical oxidation in platelets in sick calves became possible due to severe depression of the antioxidant enzymes of the blood plates - superoxide dismutase - 1250.0±4.36 IU/10^9 platelets (in healthy calves 1780.0±2.06 IU/10^9 platelets) and catalases - 5,690.0±21.0 IU/10^9 platelets (in the comparison group 10,500.0 ± 11.05 IU / 109 platelets). The content of medium molecules in plasma at 280 nanomoles was 0.49±0.01 conventional units, at 254 nanomoles - 0.32±0.02 conventional units, versus control 0.32±0.002 conventional units and 0.24±0.03 conditional units, respectively. In the platelets of calves with functional disorders of the digestive system, the medium molecules at 280 nanomoles - 0.061±0.02 conventional units/10^9 platelets, at 254 nanomoles - 0.069±0.03 conventional units/10^9 platelets (in the control 0.050±0.04 conventional units /10^9 platelets and 0.055±0.04 conventional units/10^9 platelets, respectively).

In the study of the lipid composition of platelet membranes in calves with functional digestive disorders, a decrease in total phospholipid content to 0.38±0.001 μmol/10^9 platelets and an increase in cholesterol level to 0.82±0.001 μmol/10^9 platelets was found. In healthy animals, similar indicators were at the level of 0.49±0.002 μmol/10^9 platelets and 0.73±0.001 μmol/10^9 platelets, respectively. In animals with functional disorders of the digestive system, increased thromboplastin formation was detected. At the same time, the generation time of active thromboplastin was 2.95±0.01 minutes with an activity of 9.6±0.02 s. In the control group, thromboplastin was formed in 2.40±0.01 min, and its activity was 14.0±0.05 s.

In newborn calves with functional digestive disorders in platelets, increased exchange of arachidonic acid was registered with an increase in thromboxane formation. According to the results of a simple transfer test, an increase in the level of thromboxane in the blood plates of calves was found to - 74.3±0.03% (in the control - 39.2±0.02%). At the same time, this growth was possible due to the activation of cyclooxygenase, established for the restoration of antibodies in the collagen-aspirin test - 96.8±0.05% and thromboxane synthetase for the reduction of antibodies in the collagen-imidazole test - 54.6±0.02%. In newborn calves with a deviation in health status, these figures were 78.4±0.19% and 30.3±0.01%, respectively.

The content of platelets in the blood of calves with functional disorders of the digestive system was within the normal range. At the same time, they recorded an acceleration of AP, especially under the influence of collagen - 25.3±0.20 s (in the control - 30.0±0.12 s). The slower AP in calves was under the action of ADP (33.0±0.12 s) and ristomycin (26.2±0.13 s) at a control level of 39.0±0.28 s and 41.0±0.26 s, respectively. Thrombin and adrenal AP in newborn calves with functional digestive disorders also developed faster than in control and were at 42.4±0.11 s and 75.6±0.16 s, respectively ($p<0.01$). The development time of AP with the combined use of inductors was even more accelerated than with their isolated application, exceeding the level of control - ADP + adrenaline - 20.0±0.12 s., ADP + collagen - 18.0±0.09 s., adrenaline + collagen - 20.3±0.07 s.

In calves with functional digestive disorders on the background of venous occlusion, AP was slowed down, most pronounced with adrenaline - IAAVW 1.30±0.06 s (in the control - 1.65±0.02 s). Slightly smaller IAAVW were registered with H_2O_2 (1.27±0.07), ristomycin (1.28±0.06) and ADP (1.22±0.05). At the same time, IAAVW with thrombin and collagen were in a state of even greater depression - 1.18±0.12 and 1.17±0.11, respectively. The indices of antiaggregatory activity of the vascular wall using combinations of inductors were significantly lower than the control: with ADP + adrenaline 1.25±0.03 s., ADP + collagen - 1.24±0.01 s., adrenaline + collagen - 1.16±0.07c.

The intravascular activity of platelets in newborn calves with functional digestive disorders was increased. The content in the blood of inactive forms of blood plates - discocytes in calves with functional digestive disorders was 62.0±0.20% (in the control - 82.0±0.16%). This was accompanied by an increase in the bloodstream of the number of disco-echinocytes (18.0±0.40%), spherocytes (12.0±0.03%), sphero-echinocytes (6.0±0.02%) and bipolar platelet forms (2.0±0.01%) also significantly exceeding the control values. The sum of active platelet forms of calves with functional digestive disorders was equal to 38.0±0.30%, with the level in the control being 18.0±0.20%. Small and large aggregates in the blood were recorded 15.2±0.06 and 4.7±0.03

per 100 free platelets (in the control - 3.6±0.04 and 0.12±0.01 per 100 free platelets) with the involvement of platelets in the aggregates in animals with functional digestive disorders 14.6±0.02%, versus 5.0±0.20% in the control.

DISCUSSION

Functional disorders of the digestive system are often accompanied by the development of thrombocytopathy [15,16], leading to activation of the blood clotting process [17,18]. The course of functional disorders of digestion causes shifts in the cholesterol / phospholipid ratio [19] in platelet membranes, which together with digestive disorders and absorption causes growth in the bloodstream [20,21], and subsequently in platelets the level of medium molecules leading to a weakening of antioxidant protection of blood platelets [22,23] and an increase in the concentration of LPO products in them. At the same time, an increase in platelet activity and thromboplastin formation occurs in calves [24,25]. The growth of the blood plasma thrombogenic potential during functional disorders of the digestive system is primarily due to the activation of platelet functions, and not to an increase in the levels of various coagulation factors, including fibrinogen [26]. The increase in fibrino formation, which undoubtedly occurs during functional disorders of the digestive system, occurs primarily on the surface of activated platelets, always wearing a secondary character in relation to their adhesion and aggregation [27,28].

Changes in the composition of platelet membranes that occur during functional disorders of the digestive system, an increase in the concentration of medium molecules in them, and an increase in intraplatelet LPO leads to an increase in the intravascular activity of platelets, increasing the content of active forms of blood platelets in the bloodstream [29]. The active intravascular activity of platelets causes an increase in platelet aggregation under the influence of various inducers [30,31]. The most likely mechanisms of this enhancement can be considered activation of arachidonic acid metabolism with an increase in thromboxane formation [32], detected in transfer samples [33], and an increase in the plasma content of von Willebrand factor participating in the aggregation process [34] indirectly estimated by accelerating AP with ristomitsin [35].

All animals with functional disorders of the digestive system showed a significant decrease in IAAVW compared with healthy calves, which is associated with a weakening of the production of antiplatelet agents in the vessel walls and, above all, prostacyclin [36].

The course of functional disorders of the digestive system, having a complex nature, is accompanied not only by thrombocytopathy, but also by the development of vasopathy with a weakening of the antiaggregatory activity of the vascular wall, leading to an increase in intravascular AP [37,38]. High platelet aggregation activity under the influence of various inducers indicates an increased activity of platelets in vivo [39,40]. Under these conditions, depression of arachidonic acid metabolism develops in the vessel wall, where its main metabolite is a vasodilator and an antiplatelet agent, prostacyclin, which is the main physiological antagonist of thromboxane [41,42].

The combined effect of several inductors on the AP process without venous occlusion and against its background in newborn calves with functional digestive disorders showed the reciprocal potentiating effect of agonists on platelets with a low sensitivity of the latter to disaggregating signals of the vascular wall in actual blood flow conditions [43,44]. Evaluation of AP against the background of temporary venous occlusion and without it under the influence of various combinations of inductors brings us closer to understanding the processes actually occurring in the bloodstream in newborn calves with functional disorders of digestion with dyspepsia and indicates a high risk of thrombosis in them [45,46,47].

Dysfunctions of primary hemostasis in calves with functional disorders of the digestive system require effective correction [48,49,51], aimed at breaking the “vicious circles” observed in functional disorders of the digestive system [52,23].

CONCLUSION

In newborn calves with functional digestive disorders, an increase in platelet aggregation functions in vitro and in vivo was detected.The imbalances in the lipid spectrum of platelet membranes, the increase in the

level of medium molecules in them, the activation of plasma lipid peroxidation and platelet oxidation, increased generation in the vascular wall of von Willebrand factor against the background of prostacyclinogenesis depression and intensification of platelet formation in blood plates are the basis of the revealed violations. Activation of thromboplastin formation is the leading cause of increased blood coagulation in newborn calves with functional digestive disorders. On the basis of the studies performed, it can be said that the correction of disorders of the platelet hemostasis should include a pathogenetically determined complex capable of leveling functional disorders of the digestive system and optimizing the blood rheology at the same time.

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