Research Article

Correction of the Immune Status of Cows by Using Aminoseleton During the Dry Period for Prevention of Antenatal Calf Hypotrophy

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Abstract | The article describes the indicators of secondary immune deficiency in pregnant cows during the cow drying off. Morphological, biochemical, and immunological blood parameters are displayed. Clinical manifestation of calf hypotrophy syndrome during the neonatal period is studied. The experience of using Aminoseleton for pregnant cows during the drying off is describes. Evaluation of the biological effect on the organism of cows of a new tissue biostimulator was carried out on 22 cows with secondary immunodeficiency 30-45 days before calving, formed on the principle of paired analogues in two groups. Aminoseleton was used subcutaneously five times every 72 hours at a dose of 40 ml. The positive effect of immunomodulator Aminoseleton on metabolic status and the overall non-specific resistance indicators during the cow drying off was revealed. According to the results hypotrophic calves were born with a deficiency of body weight and a non-proportional physique. Tendency to centralize circulation, hypovolemia, hyperdynamic reaction with infarction, pulmonary hypertension with, spastic condition precapillary arterioles, disturbance of microcirculation in microvessels in newborn hypotrophic calves was observed. In perinatal hypotrophy in calves, inhibition of cellular immunity was noted predominantly against the background of an increased activity of oxidative metabolism in neutrophils. The results of our research indicate a violation of the structure and links of non-specific cellular and humoral resistance in calves with perinatal hypotrophy. As a result, a direct correlation between the level of non-specific resistance of the mother's organism, and the state of health condition of the newborns is established.

Keywords | Cow, Prevention, Hypotrophy, Calf, Metabolism.

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INTRODUCTION

Neonatology of animals remains one of the least studied branches of biological science, at the same time, illness of newborns among productive animals are fairly widespread (Shakhov et al., 2005; Golubtsov et al., 2015; Lenchenko et al., 2017; Suleymanov et al., 2018). Such animals are characterized by a pronounced lag in growth and development, as well as a wide spectrum of homeostatic and morphofunctional characteristics (Savrasov and Parshin 2012; Dronov, 2013; Shakhov et al; 2013; Nezhdanov et al., 2014).

A direct relationship has been established between the level of nonspecific resistance of the mother's body, on the one hand, and the intrauterine development of the embryo, the state of health and the safety of newborns, on the other. For example, calves obtained from cows with sub-

clinical pathology have signs of intrauterine malnutrition, among them - underdevelopment of organs and systems, high morbidity and mortality. Under stress, endocrine organs are primarily involved in the process of structural and functional changes. Immunocompetent organs are depressed, and the degree of colostrum passive immunization is insufficient due to the low content of immunoglobulins in the colostrum of such mothers. Thus, immunodeficiency states develop.

Aminoseleton is a tissue preparation based on the hydrophilic fraction of cattle spleen obtained by cryofractionation, which has immunomodulating, antioxidant, adaptogenic, actoprotective, stress-correcting effects. The drug is a biologically active substance with the most fully preserved native structure of a wide range of biologically active substances (proteins, vitamins, minerals, phospholipids, etc.). Having an endogenous origin, they provide optimal physiological correction, act quickly, without causing side effects. Despite the improvement of specific prophylaxis, means of immune modulation and protection, a system of measures to prevent and combat bacterial and viral diseases, the problem of preserving and reducing the incidence of newborns remains one of the most actual problems (Bryantsev, 2000; Sidorova et al., 2000; Kurylenko et al., 2006; Foote et al., 2007; Vasilenko, 2008; Osorio et al., 2013). Organism need special attention and care in the neonatal period. During the period when newborn organism adapts to new conditions the structural organization of cells and tissues of the most critical systems activates, providing the support of livelihoods (Briassoulis et al., 2001; Shabalov, 2006; Shabalov, 2011; Ballou, 2012). The inferiority of the structural organization of the digestive, endocrine, immune and other body systems of the newborns determines the occurrence of pathology (Chandra, 1997; Gernaat and Voorhoeve, 2000; Colomb, 2003; Lenchenko et al., 2019).

Many researchers have reported a decrease in the nonspecific immunity of young cattle during stress exposure characterized by a decrease in the lysozyme concentration of saliva, nasal and bronchial mucus, low phagocytic activity and serum complement, increase (more than 1.2 times) of the natural inhibitory factor of macromolecular antibodies (Ig M), as well as factors of humoral immunity. It results less protection against infections (Griebel et al., 1987; Hülst et al., 2004; Savrasov and Parshin, 2012; Seleznev et al., 2017).

At all stages of fetal development, especially during the last months of intrauterine life, an important factor is the complete nutrition of the maternal animals (Schoonderwoerd et al., 1986; Shakhov, 2005; Foote et al., 2007; Golubtsov et al., 2015). Under unfavorable conditions of the course of pregnancy, with insufficient and inadequate feeding of pregnant cows, calves are born with hypotrophy. Hypotrophy reflects the concept of "physiological immaturity" of newborns, it is sometimes called the "syndrome of weak calves" (Kuzminova EV et al., 2011).

One of the promising approaches to overcome hypotrophic births is the use of drugs based on proteins (amino acids), which have a positive effect on health, improve metabolic processes, physiological and biochemical parameters, resistance and productivity of animals. Active intervention in the metabolism of proteins can change the course of the pathological process - to stimulate the emergence and proliferation of living matter or to stop the process of extinction of living matter (Shakhov et al., 2005; Kurylenko et al., 2006; Korobov et al., 2007; Gromov et al., 2008).

Hypotrophic births causes significant economic damage, which is characterized by weight loss, mortality and forced culling of animals.

Hence, the purpose of current research was to study the effect of Aminoseleton on the immune status of pregnant cows during the dry period for the prevention of antenatal hypotrophies of calves.

MATERIALS AND METHODS

Ethical Approval

The present studies were carried out in accordance with the State program of Peoples' Friendship University of Russia (RUDN University). Research on animals was conducted after receiving approval of Bioethics commission SREC PFUR.

Experimental Animals

The studies were performed on Holstein-Friesian cows belonging to the OOO Voronezhpischeproduct of the Novousmansky district of the Voronezh region. 30 cows 30-45 days before calving were selected as objective of the study. Blood tests were performed on all cows. Secondary immunodeficiency was detected in 22 animals. Evaluation of the biological effect of a new tissue biostimulator (Aminoseleton) was carried out on the cows with secondary immunodeficiency, formed on the principle of paired analogues in two groups.

In cows of the first (experimental) group (n = 11) Aminoseleton was used subcutaneously five times every 72 hours in increasing doses: 30-35-40-45-50 ml, while in cows of the second (Control) group (n = 11) the drug was not applied. Before the introduction of the drug and 5-7 days after the last injection, blood was obtained from the cows of both groups (n = 22) for morphological and biochemical studies in order to assess the effect of the drug on the immunobiological resistance of their body. Animals are selected in the

group according to the method of paired counterparts, the same age, body weight, on the second period of lactation. The maintenance, feeding, treatment of dry cows of experimental and control groups is typical for the household.

From all animals of the experimental and control groups received newborn calves. In order to assess the effectiveness of preventive measures, all newborn calves were divided into two groups, according to the numbers of groups of mother-cows from which they were obtained. Newborn calves of the first group are from cows of the experimental group, newborn calves of the second group are from cows of the control group that did not receive Aminoseleton, in each group of 11 animals.

Observation

After parturition the calves from both groups of cows (Aminoseleton treated and Control) were separated. The determination of the clinical status of newborn calves was carried out in the first hours after birth. A clinical study for all calves was carried out throughout the prophylactic period (15 days), according to the generally accepted plan in veterinary medicine. The main criteria for assessing the condition of the body of newborn calves were: pulse rate in 1 min., respiration rate in 1 min, color of visible mucous membranes, muscle tone and reflex excitability. Their zoometric parameters were also taken into account: body weight at birth, height at withers, slanting body length, chest girth behind the shoulder blades, average daily weight gain, and the amount of colostrum drunk.

Morphological blood analysis in cows and calves was performed on a hematology analyzer ABC Micros 60, biochemical studies (Hitachi-902 analyzer) and medium molecular peptides (MMP) were performed in accordance with the methodological recommendations (Shakhov, 2005). Immunomodulatory indicators, including complementary (SCA) and lysozyme (SLA) activity, total immunoglobulins (Ig), circulating immune complexes (CIC) in serum (humoral serum factors of non-specific immunity), endogenous intoxication index (EII) and the number of T- and B-lymphocytes (cellular immunity), were determined using standard and unified methods (Shakhov, 2005).

Statistical Analysis

Statistical processing of the obtained data was performed using the Statistica 6.1 software package (StatSoft, Inc., USA). The research results are presented as mean (M) and standard mean error (± SEM). The significance of differences between treatment and control was assessed by Student's t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Changes in Blood Parameters After the Use of Aminoseleton

During this experiment it was found that the cows treated with Aminoseleton exhibited a positive increase in leukocyte count (13.8%; $P < 0.01$), monocytes (41.4%; $P < 0.001$), band neutrophils (35.5%; $P < 0.001$), in comparison with control animals during 7.5-8.0 months of gestation period (Table 1). Likewise, total protein by 5.4%, α-globulin fraction of protein by 10.7% and β-globulin by 16.4% was improved by treatment of Aminoseleton as compared to control group animals which indicates a significant improvement in general nonspecific immunity of the body before calving. In control animals, we found an increase in eosinophil content by 1.8 times ($P < 0.002$), segmented neutrophils by 27.0% ($P < 0.01$), total immunoglobulins by 13.2% ($P < 0.05$), γ-globulins by 10.7%, circulating immune complexes 1.6 times, endogenous intoxication index 2.8 times ($P < 0.001$), average molecular peptides 1.8 times ($P < 0.002$), with a decrease in lymphocytes by 20.8% ($P < 0.001$), which indicates the beginning of the development of the inflammatory process in the body of cows before calving. In animals of the control group before calving changes in blood indices witnessed that, they increased the antigenic load on the body of dry cows, increased allergization, and intense functioning of the lipid peroxidation system with a decrease in the indices of general nonspecific immunity (Merzlenko and Kurtov, 2003).

Hypotrophy Development in Newborn Calves

Antenatal hypotrophy is a pathology of the fetus, manifested by impaired fetal development and a pathophysiological reaction to an insufficient supply of oxygen to the fetus (Merzlenko and Kurtov, 2003; Tochina et al., 2008). The birth of physiologically immature young animals is associated with impaired growth and development in the prenatal period. In calves with a syndrome of hypotrophy, the body's resistance to infectious disease is reduced, due to the lag in the formation of humoral and cellular factors of natural resistance, which in turn contributes to the development of gastrointestinal, respiratory and other diseases in the late period of animal's life. In addition, hypotrophy in calves is accompanied by the development of secondary immune deficiency, which also exacerbates the age-related immune deficiency and thereby inhibits erythropoiesis, disrupting all parts of the metabolic process in the body (Bryantsev, 2000; Amesty-Valbuena and Pereira, 2004; Hülst et al., 2004; Shakhov, 2005; Romensky et al., 2013).

In order to assess the effect of Aminoseleton we studied newborn calves obtained from cows-mothers of the control and experimental groups. According to the results hy potrophic calves were born with an average body weight

Table 1: Changes in blood parameters of cows at 7.5-8 months of pregnancy

Indicators	Reference Values	12 days after treatment	
		Aminoseleton treated group (n=11)	Control group (n=11)
Leukocyte, 10^9/L	4.5-12.0	7.4±0.8	6.5±0.25
Eosinophils, %	5-8	5.8±1.4	10.7±0.27
Band neutrophils	2-5	4.8±0.33	3.1±0.29
Segmented neutrophils	20-35	27.2±1.8	37.3±2.59
Monocytes, %	2-7	4.1±0.19	2.9±0.21
Lymphocytes, %	40-60	57.7±1.1	45.7±1.79
Total Protein, g/l	70-85	76.2±3.7	72.1±2.7
Albumins, %	26.5-35.0	57.1±3.1	57.7±1.97*
α- globulins, %	12-20	10.3±0.49	9.2±0.38*
β- globulins, %	10-16	19.5±1.44	16.3±0.91*
γ- globulins, %	23.5-40	17.5±1.44	19.6±1.3*
Total Jg, g/l	25-30	24.41±1.29	28.12±1.5
CIC, g/l	0.20-0.40	0.17±0.03	0.27±0.01
SBA, %	50-85	62.02±3.7	59.71±2.9
SLA, μg/ml	0.6-25	0.23±0.02	0.31±0.03
EII, c.u.	3.0-16.0	2.1±0.2	6.0±0.29
MMP, c.u.	0.70-0.90	0.24±0.02	0.44±0.03

* Showing significant difference between the groups at P≤0,001-0,05

CIC - circulating immune complexes, SBA - serum bactericidal activity, SLA - serum lysozyme activity, EII - endogenous intoxication index, MMP - medium molecular peptides

Table 2: Morphological and biochemical blood parameters of calves born from cows of Aminoseleton treated (normotrophic) and control group (hypotrophic)

Indicators	Aminoseleton treated group (n=11)	Control group group (n=11)	Reference values
Erythrocytes (RBC), 10^{12}/l	6.92±0.23	7.98±0.18	5.7-9.3
Hemoglobin (Hb), g/l	96.0±6.1	131.0±7.2	105.0-126.0
Color indicator (MCHC)	0.69±0.03	0.92±0.13*	0.9-1.1
Leukocytes, 10^9/l	8.7±0.5	11.1±0.3	7.2-12.1
Specific gravity, c.e.	1.071±0.019	1.045±0.012	1.05-1.06
Blood viscosity	5.97±0.09	4.77±0.12	4.2-5.2
Total protein, g/l	59.4±1.8	71.33.2	54.9-57.1
Albumins, g/l	16.7±1.2	23.3±2.1	22.5-24.9
α- globulins, g/l	10.9±0.2*	9.1±2.1	8.7-11.5
β- globulins, g/l	6.9±0.7*	8.9±1.3	8.4-10.4
γ- globulins, g/l	15.9±0.9*	17.8±1.1	17.2-18.2
T- lymphocytes,10^9/l	1.10±0.15	1.51±0.17	0.9-4
B- lymphocytes,10^9/l	0.47±0.11	0.69±0.07	0.4-1.5
SBA, %	49.1±1.4*	67.7±1.3	89-100
SLA, μg/ml	1.27±0.13*	0.33±0.12	0.3-0.5
SCA, % haem	0.83±0.12*	1.65±0.12	1.5-3.0
Vitamin A, umol/l	0.3±0.02	0.4±0.04	0.4-1.5
Total lipids, g/l	2.28±0.14	2.02±0.15	1.46-2.10

Cholesterol, mmol /l	1.97±0.05	1.65±0.07	1.23-1.73
Triglycerides, mmol/l	0.41±0.03	0.12±0.01	0.09-0.38

* Showing significant difference between the groups at P≤0,001-0,05
SBA - serum bactericidal activity, SLA - serum lysozyme activity, SCA - serum complementary activity

deficiency of 30.2% and a disproportionate physique compared with clinically healthy animals. The main zoometric indices in hypotrophic calves were: the slanting body length, height at the withers, and chest girth behind the shoulder blades were below the physiological limits, by an average of 11%. In diseased calves, a depression of the motor-digestive reflex was observed, which was delayed by 1.5-2 hours, the number of sucking movements decreased by a factor of 1.5 in one minute. Milk teeth are in some cases underdeveloped. The subcutaneous fat layer on the abdomen and other parts of the body is thinned. Visible mucous membranes are anemic. The eyeball is sunken. Auricles and tail are saggy. The local temperature on the skin surface of the body is unevenly distributed: higher in the front and lower in the back.

The respiratory system was diagnosed with tachypnea, arrhythmic and shallow breathing. On the part of the cardiovascular system, tachycardia was diagnosed in 60.0% of the calves in the control group, in 40% bradycardia, muffled heart tones. For the cardiovascular system in newborn hypotrophic calves, there is a tendency to centralize blood circulation against hypovolemia, hyperdynamic myocardial reaction, pulmonary hypertension, spastic condition of precapillary arterioles, impairment of microhemocirculation in microvessels.

Morphological and Biochemical Blood Parameters of Calves With Normotrophy and Hypotrophy

In the clinical assessment of the nervous system, a decrease in neuromuscular tone was noted: calves with perinatal hypotrophy rely poorly on limbs, movements are unsure, animals were in a forced lying position. Pinch response has shown hyperalgesia and reduced tactile sensitivity; it was noted lability-oppression (apathy) which was replaced by arousal.

Table 2 exhibited that, when evaluating the morphological parameters of blood in calves of the experimental group, the number of erythrocytes was 7.89 ± 0.41·10^{12} / l, and in hypotrophic calves from the control group erythropenia was observed (6.92 ± 0.23·10^{12} / l erythrocytes). The amount of hemoglobin in the blood: in clinically healthy calves of the experimental group, 131.0 ± 7.24 g / l; in hypotrophic calves of the control group 96.0 ± 6.11 g / l. A color indicator of blood in sick calves, in contrast to healthy ones, was <1. Diagnosed with impaired leukopoiesis: in clinically healthy calves, the number of leukocytes was 11.1 ± 0.35·10^{9} / l, in calves with hypotrophia, leukopenia was observed 8.7 ± 0.55·10^{9} / l. An absolute lymphopenia was established during morphological blood examination in hypothrophic calves. Blood specific gravity was 1.071 ± 0.019, blood viscosity was 5.97 ± 0.09. The content of total protein in serum was 59.4 ± 1.8 g / l, which is 20.0% lower than that of physiologically mature calves. In calves with antenatal hypotrophy albumin, β- and γ-globulin fractions were respectively lower by 28.0% (P <0.001), 22.4% (P <0.001) and 10.2% (P <0.05), and α -globulin higher by 14.3% (P <0.01), compared with the animals of the experimental group. The number of T- and B-lymphocytes in the hypotrophic calves of the control group was 26.6% (P <0.01) and 31.4% (P <0.01) respectively. The serum bactericidal activity (SBA) and serum lysozyme activity (SLA) in the first days of life in calves with perinatal hypotrophy were higher by 17.7%, 183.6%; whereas, the rate of complementary serum activity (CSA) was lower in 2 times (P <0.01). In case of the disease of calves with perinatal hypotrophy, predominantly inhibition of cellular immunity was noted against the background of an increase in the activity of oxidative metabolism in neutrophils. The results of our research indicate a deteriorating effect of perinatal hypotrophy on nonspecific cellular and humoral immunity of the calves.

It is well recognized that the relationship between mother and fetus play an important role in the occurrence of diseases of the newborn calves. Various diseases and metabolic pathologies in the mother's body, placental insufficiency and several other factors cause serious abnormalities in the fetus's body, and subsequently they affect the viability of the newborn animal and its growth process (Savrasov et al., 2012; Nezhdanov et al., 2014). Researches have declared that, the cause of these disorders is the inadequate feeding of cows during pregnancy. Usually, this is understood as a deficiency in the diet of protein or carbohydrates, non-compliance with the optimal ratio between them, poor-quality food, lack of macromineral substances and vitamins (Foote et al., 2003; Osorio et al., 2013).

Indicators of carbohydrate-vitamin metabolism in hypotrophic calves were also below the physiological limits. The content of vitamin A was lower by 18.0% compared with the calves with normotrophy. The level of total lipids, cholesterol esters (EC) and triglycerides (TG) were higher than the reference values in calves of the control group by 11.2% (P <0.01), 16.3% (P <0.01) and 69.7% (P <0.01), respectively (Table 2). Hyperlipidemia in calves with antenatal hypotrophy due to TG and EH indicates the reor-

ganization of the body's metabolism from carbohydrate to lipid which is a manifestation of stress reaction (Golubtsov et al., 2015).

As a result, we found that calves (11 animals) obtained from pregnant cows of the control group were born with antenatal hypotrophy, and calves from the experimental group (11 animals) were normotrophic (Table 3). According to our observations, the incidence of gastrointestinal hypothrophy calves during the trial period was 80.0%. Of the cases, 25.0% fell. The safety of young animals in the control group was 80.0%. In the experimental group, the incidence of gastrointestinal diseases was 18.2%, the mortality rate from the number of cases was 0%, and the safety was 100%. Calves of the Aminoseleton treated group had a slight form of dyspepsia and later grew and developed in accordance with the breed criteria. Subcutaneous administration to the cows of the experimental group during the launch of the tissue biostimulator-aminoseleton, by 100.0%, reduced the birth rate of calves with prenatal malnutrition syndrome. In the neonatal period, by 55.0% of the control, the incidence of calves with gastrointestinal diseases decreased.

Table 3: Indicators of preservation of calves

Indicators	Aminoseleton treated group (n=11)	Control group group (n=11)
Number of animals, heads	11	11
Calves born, heads	11	10
Body weight, kg	39,3±1,8	28,1±1,4
Hypotrophic calves, heads	0	10
Diseased calves, heads	2(18,2)	8 (80,0)
Fallen calves, heads	0	2 (20,0)

CONCLUSION

Thus, our research allows us to conclude that the use of Aminoseleton in pregnant cows during the dry period results significant improvement in their metabolic status, an increase in the overall nonspecific immunity, the formation of a physiologically mature fetus (that indicated by a higher level of homeostasis in the body of newborn calves) and a reduction in the risk of antenatal hypotrophy.

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CONFLICT OF INTEREST

We declare that authors have no competing interests.

AUTHORS CONTRIBUTION

The authors contributed equally.

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