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ORIGINAL ARTICLE

Effect of Butaselmevit-Plus on the immune system of piglets during and after weaning

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The aim of our research was to study the effect of Butaselmevit-Plus feed additive on the immune system indexes of piglets during weaning. The study was conducted at Koshet LLC in Mukachevo Raion of Zakarpattia Oblast. We formed two groups of piglets: control (C) and treatment (T) with 10 individuals in each group selected on the basis of analogues – age, breed, and body weight. The animals received nutrition according to the norms for pigs of this age. On the 28th day after birth, the piglets were separated from the saw. Piglets from different litters were rearranged for further wean-to finish maintenance with changes in diet. This period is stressful for the animals. From the age of 5 days, piglets of all groups were fed with pre-starter feed. From the age of 21 to 40 days, piglets of the experimental group received additionally Butaselmevit plus at a dose of 100 mg/kg of body weight per day. Our research material was the blood collected in the morning before feeding. The blood was taken by cranial vena cava puncture – on the 20th day of life (period before weaning), on the 25th day of life (period before weaning), on the 30th day of life (2nd day after weaning), on the 35th day of life (7th day after weaning), and on the 40th day of life (12th day after weaning). Butaselmevit-Plus feed additive contributes to the increase of the number of T and B-lymphocytes in blood of piglets. Components of Butaselmevit-Plus promote activation of the cellular immune system of piglets before and after weaning. Introduced additionally, Butaselmevit-Plus also boosts functional activity of immune competent cells in piglets after weaning. This happens in the result of the redistribution of T and B-lymphocytes receptor apparatus that increases the lymphocytes avidity. When feeding Butaselmevit-Plus to piglets during weaning, we observed the increase in humoral component levels of the immune system during the whole period of study. On the 35th day of life, the treatment group of piglets with Butaselmevit-Plus showed 4.26% increase in neutrophil phagocytic activity. We also observed an increase in phagocyte number and phagocytic index of the pigs in the treatment group – on the 35th day of the experiment the indexes of treatment group exceeded the indexes of control group by 7.5% and 11.2% correspondingly.
Keywords: pigs, stress, Butaselmevit-Plus, feed additive, immune system.

Introduction

Homeostasis of the internal environment of the animal body depends primarily on the interconnection of the individual units of the metabolic processes and the lability of the components taking part in the common system (Ahmad et al., 2011; Petrukh et al., 2015; Gutyj et al., 2018; Holovakha et al., 2018; Lieshchova et al., 2018; Slivinska et al., 2019; Yevstafieva et al., 2019). Blood responds to any exogenous or endogenous influence on the organism by changing its quantitative and qualitative composition. Therefore, blood is a kind of biomarker that allows to determine the overall condition of organs and systems and to evaluate the course of major metabolic processes (Chala & Rusak, 2016; Martyshuk et al., 2016; Kozak & Brygadyrenko, 2018; Kulyaba et al., 2019; Kushnir et al., 2019). For this reason, the analysis of biochemical parameters of blood – especially the indicators of animal's immune system – is one of the informative methods that allows to define the transition from norm to pathology.

During the recent years, preparations and feed additives based on vegetable raw materials have been widely used to enhance the protective systems of the animal body under oxidative stress (Cherkashina & Petrenko, 2006; Skrypnyk, 2007; Saba et al., 2010; Zhukova et al., 2016; Gutyj et al., 2017). The potentially prospective preventive herbal medications for environmentally caused animal immunodeficiencies are Echinacea, lemongrass fruit, and ginseng root. According to the recent studies, the most promising immune stimulator is Saint-Mary-thistle *Silybum marianum* (Khariv et al., 2016; Khariv et al., 2017; Gutyj et al., 2019). Selenium preparations are the most common biologically active additives. Due to the increased technogenic influence on animals (Sobolev et al., 2017), the study of the interaction of selenium and other trace elements normalized in the diets is particularly important nowadays. Thus, intensive

development of animal breeding requires new approaches to nutrition of farm animals. Introducing new feed additives as supplements to feed and water helps to improve their nutritional value, increase productivity and general animal welfare (Kotsumbas & Hryniv, 2016; Danchuk et al., 2019).

The aim of our study was to analyze the influence of feed additive Butaselmevit-Plus on the immune indexes of piglets before, during and after weaning.

Material and methods

The research was conducted at Koshet LLC in Mukachevo Raion (Region) of Zakarpattia Oblast (Ukraine). We formed two groups of piglets – control (C) and treatment (T) with 10 individuals in each group selected on the basis of analogues – age, breed, and body weight. During the suckling period the piglets were kept near sows in special crates, had constant access to the saw and free access to concentrated feed (from the age of 5 days). The piglets were fed in accordance with the nutrition requirements for their age. Clinical and physiological examinations of piglets were conducted prior to the study. We took into account general condition and activity of piglets while eating. On the 28th day of life the piglets were separated from the saws. Piglets from different litters were rearranged for further wean-to finish maintenance with changes in diet - a technological stress for the animals. From the age of 5 days piglets of all groups received pre-starter feed. From the 21st to the 40th day of life Piglets of the treatment group received Butaselmevit-Plus feed additive in a dose of 100 m/kg body weight per day.

Our research material was the blood collected in the morning before feeding. The blood was taken by cranial vena cava puncture – on the 20th day of life (period before weaning), on the 25th day of life (period before weaning), on the 30th day of life (2nd day after weaning), on the 35th day of life (7th day after weaning), and on the 40th day of life (12th day after weaning).

Serum lysozyme activity was determined by the nephelometric method using test microbe *Micrococcus lysodeicticus* BKM-109, the optical density was measured at a wavelength of 540 nm. Serum bactericidal activity in samples was evaluated according to Y. M. Makarov (1968) using overnight culture *E. Coli* BKM-125. Photocolorimetry was performed before and after 3-hour incubation (Vlizlo et al., 2012).

The level of circulating immune complexes in serum was determined using borate buffer. Selective precipitation of antigen-antibody complexes took place under the influence of high molecular weight PEG with the mass of 6000 Da. The results were evaluated by photocolorimetry of the precipitate density at a wavelength of 450 nm (Vlizlo et al., 2012).

The phagocytic response of blood neutrophils was evaluated according to phagocitic activity (PA), phagocytic index (PI) and phagocyte number (PN) according to B.S. Gostev (1950). Stabilized blood was incubated with overnight culture of *E. coli* BKM-125. The smears were examined under a microscope in an immersion system. PA was determined by the number of active neutrophils in 100 of cells calculated, PI – by the number of microbial bodies phagocytosed by one active neutrophil, PN – by the number of phagocytosed microbial bodies per 100 of calculated neutrophils (Vlizlo et al., 2012). The number of T-lymphocytes was determined in the reaction of spontaneous rosette formation with erythrocytes of ram according to the method described (Vlizlo et al., 2012). There were active rosette-forming lymphocytes with receptors capable of attaching ram erythrocytes without incubation, Theophylline-resistant (TER) helper lymphocytes that form rosettes after incubation with Theophylline (Vlizlo et al., 2012). To determine B-lymphocytes, we prepared EAC (erythrocyte-antibody-complement) system by adding hemolytic serum to the erythrocytes of a ram (Vlizlo et al., 2012). The rosettes were counted by microscopy of smears under immersion. We differentiated lymphocytes according to the density of receptors and quantity of the attached ram erythrocytes: zero – lymphocytes (undifferentiated) that did not attach any erythrocytes, low-avidity lymphocytes (poorly differentiated) with 3–5 erythrocytes attached, medium-avidity lymphocytes (average receptor density) with 6–10 erythrocytes attached, and high-avidity lymphocytes with more than 10 erythrocytes attached (Vlizlo et al., 2012).

The results were analyzed using the Statistica 6.0 software package. The significance level of difference was estimated by Student's t-test.

Results and discussion

While studying the immune system of piglets it is important to consider quantitative composition of leukocytes – particularly T and B-lymphocytes that show the level of body defense and the state of specific immunity (Khariv et al., 2017). During the immune system formation in the first three days after the birth, the piglets are protected with maternal antibodies that create passive (colostral) immunity (Stojanovskyj & Ogrodnyk, 2016). The ability of response to virtually any antigen is possible due to a large number of different populations of lymphocytes, each having specific receptors for specific antigens. T and B populations play a major role in body protection (Khariv et al., 2017).

During our study we monitored the changes in of T- and B-lymphocytes count in the blood of pigs of control and treatment groups. The total number of T lymphocytes in the blood of 20-day-old piglets ranged within 46.00 ± 1.19 and 45.92 ± 1.21%. Further on, the total number of T-lymphocytes on the 25th day of life of the piglets of the control group slightly decreased. Low number of T lymphocytes was found in blood of piglets after weaning. On the 35th day of life this index decreased by 5.79% in comparison to the beginning of the experiment (Table. 1). However, in the blood of the pigs of the control group on the 30th day of life we observed a decrease in low-avidity and medium-avidity T lymphocytes that bind 3–5 and 6–10 erythrocytes of ram. Among the 35-day-old piglets we observed 6.55% decrease in low-grade T-lymphocytes in comparison with the indexes of 20-day-old piglets. Also, there was a slight increase in the medium-avidity and high-avidity T-lymphocytes during the indicated period of the study – by 0.41 and 0.35% respectively. The 40-day-old piglets had a probably lower number of high-avidity T-lymphocytes: the piglets of the control group had 1.79 ± 0.21% and the 20-day-old pigs – 2.62 ± 0.49% (Table 1). These data show that after the end of the stressful period caused by weaning from the sow, the functional activity of T-lymphocytes in blood of the piglets decreases. Besides, the total number of low-density receptor T-lymphocyte during these periods of study was also lower than before weaning. Feeding piglets with Butaselmevit-Plus promotes the increase in the number of medium-avidity and high-avidity T-lymphocytes. In the blood of 35-day-old piglets the indexes of medium- avidity and high-avidity T-lymphocytes were higher then those of control group by 2.9 and 0.65 % respectively. Possible changes in medium and high avidity T-lymphocytes in the blood of piglets are observed in 45-day-old piglets – 5.21 ± 1.10% and 4.28 ± 0.30% for treatment group, and 5.21 ± 1.10 and 4.28 ± 0.30% for the control group.

Table 1. The number of T and B-lymphocytes and their functional activity in the blood of piglets under the effect of Butaselmevit-Plus

Index	Groups	Age, days				
		20	25	30	35	40
T - total, %	C	46.00±1.19	45.10±2.92	44.23±1.98	40.21±0.99	38.41±2.10
incl.	T	45.92±1.21	45.60±1.87	45.56±1.45	44.47±.20	43.59±2.30
low-avidity	C	37.17±1.56	36.78±1.99	36.81±1.30	30.62±1.74	31.41±1.51
(3-5)	T	37.05±2.05	35.25±0.97	33.11±1.24*	31.33±0.85	29.41±1.40
medium-avidity	C	6.21±0.50	6.11±0.75	5.64±0.82	6.62±0.60	5.21±1.10
(6-10)	T	6.14±0.61	7.21±0.53	8.98±0.77**	9.52±1.00*	9.90±.58*
high-avidity	C	2.62±0.49	2.21±0.53	1.78±0.32	2.97±0.41	1.79±0.21
M	T	2.73±0.34	3.14±0.22	3.47±0.24*	3.62±0.30	4.28±0.30***
T-active, %	C	21.62±0.75	21.56±1.02	20.87±1.10	19.62±1.57	23.54±1.60
incl.	T	21.60±0.52	22.56±0.60	23.14±0.58	24.00±0.60*	32.28±0.45***
low-avidity	C	17.38±0.70	17.43±0.98	17.36±1.05	17.29±0.85	19.47±1.15
(3-5)	T	17.35±0.49	17.85±0.84	18.81±0.35	19.42±0.65*	22.14±1.10
medium-avidity	C	4.24±0.65	4.13±0.30	3.51±0.29	2.33±0.41	4.07±0.50
(6-10)	T	4.25±0.57	4.71±0.54	4.33±0.34	4.58±0.37**	10.14±0.81**
T-helpers, %	C	23.89±0.71	23.42±1.10	22.10±1.05	19.14±1.20	22.89±0.98
incl.	T	23.84±0.80	24.11±1.25	26.71±1.12**	22.84±1.05*	26.43±1.54*
low-avidity	C	20.16±0.49	20.13±0.75	19.26±0.98	17.10±1.01	18.62±1.15
(3-5)	T	20.17±0.57	20.32±0.94	22.05±1.05*	18.23±0.65	21.70±1.30
medium-avidity	C	3.73±0.38	3.29±0.47	2.84±0.61	2.04±0.55	4.27±1.00
(6-10)	T	3.67±0.42	3.79±0.84	4.66±1.10	4.61±0.64**	4.73±0.86
suppressor T	C	22.11±1.20	21.68±3.15	22.13±2.40	21.07±1.98	15.52±2.10
cells, %	T	22.08±0.99	21.49±2.16	18.85±1.90	21.68±1.50	17.16±0.99
Immune	C	1.08±0.08	1.08±0.07	1.00±0.08	0.91±0.09	1.47±0.05
Regulation Index	T	1.07±0.05	1.12±0.02	1.42±0.08**	1.05±0.10	1.54±0.09
B lymphocytes, %	C	26.47±1.39	26.52±2.07	26.31±1.65	23.64±1.84	25.21±1.40
incl.	T	26.43±2.10	28.65±1.80	30.10±1.20	27.67±1.01*	32.44±0.95**
low-avidity	C	19.23±0.53	19.42±0.60	20.30±0.74	19.65±0.68	21.20±0.95
(3-5)	T	19.19±0.68	20.26±0.97	22.21±1.10	19.71±0.85	23.10±1.22
medium-avidity	C	7.24±1.30	7.10±0.55	6.01±0.47	3.99±0.60	4.01±0.34
(6-10)	T	7.24±0.85	8.39±0.75	7.89±0.42**	7.96±0.50***	9.34±0.74***

Notes: here and then * p<0.05;** p<0.01; *** p<0.001

During our study, we observed the decrease of T-active lymphocytes in the blood of 35 day old piglets of the control group to 19.62 ± 1.57%, including low-avidity – to 17.29 ± 0.85%. The treatment group of piglets fed with Butaselmevit-plus showed 4.38% increase of T-active lymphocytes. Also, we observed an increase in the number of low-avidity and medium-avidity lymphocytes in piglets of the treatment group by 2.13 and 2.25% respectively. We observed 1.79% decrease of the number of T-helpers in blood of piglets after weaning. The smallest number of T-helpers was found in the blood of control group on the 35th day of life with the range of 19.14 ± 1.20%, which is 4.75% less in comparison with the initial value. There was a slight increase of this indicator in the blood of 45-day-old piglets to 22.89 ± 0.98%. After receiving Butaselmevit-Plus piglets of the experimental group had an increase of T-helpers on the 30th day of the experiment, which indicates the activation of the body's immune system. Large number of T-helpers was also observed in 35- and 40-day-old piglets – it has increased by 3.7 and 3.54%, respectively.

Similar trend was observed in the number of low-avidity and medium-avidity T-helpers. We found that that in control group of piglets on the 35th day of life the number of low-avidity and medium-avidity T-helpers was the lowest – 17.10 ± 1.01% and 2.04 ± 0.55% respectively. The number of these indicators in treatment group of piglets was probably higher on the 30th and 35th day of life – by 2.79 and 1.82%, 1.13 and 2.57% respectively. Similar tendency was observed regarding T-suppressors in blood of piglets in control and treatment groups. During the whole period of study, the number of T-suppressors in the control and treatment groups decreased to 15.52 ± 2.10% and to 17.16 ± 0.99% respectively. On the 30th day of life the piglets of control group had more T-suppressors than the treatment group that received Butaselmevit-Plus. On the 35th day the quantity of T-suppressors in blood of piglets in control group fluctuated within 21.07 ± 1.98%, whereas in the experimental group it was slightly higher – 21.68 ± 1.50%. These changes in the T-cell population led to the increase of the immune regulation index of the piglets of the treatment group with Butaselmevit-Plus compared to the control group.

The study of B-lymphocytes in the blood characterizes the level of the humoral immune activity. Throughout the whole period of study the number of B-lymphocytes in the control group of weaned piglets was decreasing. The lowest number of B-lymphocytes was on the

35th day of life. It decreased by 2.83% as compared to the initial values. As to the degree of differentiation of B-lymphocytes, control group had an increase in count of low-avidity cell populations together with a decrease in the count of medium-avidity populations if compared with the indexes of the blood taken on the 20th day of life. Piglets of the treatment group that received Butaselmevit-Plus had an increase in total B-lymphocyte count, including low-avidity and middle-avidity populations. The increase of B-lymphocytes count in the treatment group comparing to the control group can be explained by the complex effect of the components of feed additive on the number of theophylline-resistant population of T-lymphocytes that activate lymphopoiesis and differentiation of b-lymphocytes.
Our studies show that Butaselmevit-Plus feed additive increases T-lymphocytes (common, active, and theophylline-sensitive) and B-lymphocytes count. It also boosts the functional activity of immune cells by redistributing the receptor apparatus of T and B-lymphocytes towards the increase of their avidity. The study of humoral immunity of piglets showed that before weaning (on the 20th day of life), BABS values (bactericidal activity of blood serum) of the control and treatment groups were within the range of 26.36 ± 0.49 and 26.10 ± 0.54% (Table 2). On the 25th day of the experiment, BABS value increased to 31.25 ± 0.87% in control and to 31.87 ± 1.02% in treatment group. Control group of piglets after weaning had 9.53 % reduction of BABS value compared to the pre-weaning indexes. BABS value of the 35 and 45-day-old piglets of control group remained at low level. BABS value in the treatment group that received Butaselmevit Plus was more higher. Thus, BABS value of the treatment group of 30-day-old piglets was 3.75% higher compared to the control group. BABS value of 35-day-old piglets was 7.36% higher compared to the control group.

Table 2. Bactericidal activity of blood serum under the influence of Butaselmevit-Plus, % (here and in Tables 3-7 the data given as M±m, n = 5)

Age, days	Groups of piglets	
	Control	treatment
20	26.36±0.49	26.10±0.54
25	31.25±0.87	31.87±1.02
30	21.72±1.10	25.47±0.68**
35	21.20±1.21	28.56±1.52**
40	22.13±0.95	27.82±1.06**

On the 20th day of the study the lysozyme activity of blood serum in control and treatment groups fluctuated within 40.49±0.75 and 40.60±0.80% respectively. 25-day-old piglets in control group had 6.36% increase of SLA (serum lysozyme activity) while piglets in the treatment group had 6.64% increase (Table 3).

Table 3. Blood serum lysozyme activity under the influence of Butaselmevit-Plus, %

Age, days	Groups of piglets	
	Control	treatment
20	40.49±0.75	40.60±080
25	46.85±0.84	47.24±2.21
30	42.87±0.97	49.46±1.50**
35	40.54±1.80	50.10±2.00**
40	41.50±2.10	49.67±2.40*

According to the data received, weaning results in the decrease of SLA in the control group of piglets on the 30th and the 35th day of the study by 3.98 and 6.31%. All 30-day-old piglets had SLA level within 49.46±1.50%, and 35-day-old piglets – 50.10±2.00%, which is 6.59 and 9.56% higher compared to the control.
On the 30th day of the study, the level of CIC (circulating immune complexes) in blood of piglets of control group after weaning was 12.9% higher than in pre-weaning period. Thereafter, even though the quantity of CIC in control group of piglets slightly decreased it still remained at a high level. Treatment group of pigs that received Butaselmevit-plus feed additive showed 7.8 and 9.3% decrease in CIC level on the 30th and 35th day of the study respectively, compared to control group of pigs.

Table 4. Circulating immune complexes in blood of piglets under the effect of Butaselmevit-Plus, mmol/L

Age, days	Groups of piglets	
	control	Treatment
20	71.24±2.04	71.42±2. 06
25	72.35±2.10	72.29±1.85
30	81.65±1.75	75.32±2.30*
35	80.84±2.20	73.36±1.94*
40	80.41±2.48	73.25±2.46*

Generally, the data obtained showed inhibitory effect of stress on the indexes of natural resistance, especially on humoral factors of protection in piglets. Butaselmevit-Plus proved its efficiency in normalizing the detected disorders. Together with the decrease of the humoral level of immune activity in weaned piglets, we observed suppression of nonspecific immune system, manifested by a decrease in phagocytic activity and phagocyte number. At the beginning of the study, the piglets of control and tereatment groups had phagocytic activity of neutrophils and phagocytic index within 45.42 ± 0.90%, 45.35 ± 0.57% and 7.35 ± 0.09 7.31 ± 0.09 units. After weaning, the piglets of control group showed 2.81 % reduction in phagocytic activity of neutrophils comparing to the initial values (Table 5). We also observed a slight raise of phagocytic index in blood of piglets of the control group and it was 7.48±0.10 units.

Table 5. Phagocytic activity of neutrophils in blood of piglets under the effect of Butaselmevit-Plus,%

Age, days	Groups of piglets	
	control	Treatment
20	45.42±0.90	45.35±0.57
25	45.67±0.85	45.74±0.65
30	42.86±1.01	47.12±1.15**
35	41.21±0.94	48.84±0.85***
40	48.54±0.59	50.94±1.00*

Table 6. Phagocytic index of the blood of piglets under the effect of Butaselmevit-Plus, units

Age, days	Groups of piglets	
	control	treatment
20	7.35±0.11	7.31±0.09
25	7.40±0.15	7.46±0.11
30	7.48±0.10	7.50±0.06
35	7.62±0.14	8.47±0.10*
40	7.60±0.20	8.11±0.12*

Feeding piglets with Butaselmevit-Plus resulted in activation of phagocytosis Thus, on the 30th day of the study phagocytic activity of neutrophils in blood of piglets of the treatment group was 4.26% higher than in control.

Table 7. Phagocyte number of blood of piglets under the effect of Butaselmevit-Plus, units

Age, days	Groups of piglets	
	control	treatment
20	3.90±0.12	4.00±0.10
25	3.98±0.11	4.11±0.12
30	3.45±0.12	3.87±0.08**
35	4.00±0.14	4.30±0.13
40	4.12±0.11	4.67±0.13**

Similar differences were obtained regarding the effect of Butaselmevit-Plus on FC and FI, particularly regarding the piglets of the experimental group. On the 35th day of the experiment, FC and FI were 7.5 and 11.2% greater than in the control (Table 6 and 7). The above-mentioned data indicate the stimulating effect of Butaselmevit-Plus on phagocytic activity by enhancing the antimicrobial properties of blood cells. Thus, weaning piglets from sows in the age of 28 days leads to inhibition of the humoral link of natural resistance. Feed additive in the treatment group boosted bactericidal and lysozyme activity of blood serum, phagocytic activity of neutrophils and phagocytic number during the weaning period. Adding Butaselmevit-Plus into feed results in the increase of the number of T-lymphocytes (common, active and theophylline-sensitive) and B-lymphocytes and boosts the functional activity of immunocompetent cells.

Conclusion

Using feed additive in treatment group contributed to the increase of bactericidal (by 7.36%) and lysozyme activity of blood serum (by 9.56%), boosted phagocytic activity of neutrophils (by 7.63%) and increased phagocytic number (by 13.3%) during the weaning period. Also, adding Butaselmevit-Plus to feed results in the increase of the number of T-lymphocytes (common, active and theophylline-sensitive) and B-lymphocytes and boosts the functional activity of immunocompetent cells.
Our future research will be focused on antioxidant protection of piglets during weaning.

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