

The effect of the drug “Bendamine” on the clinical and morphological parameters of dogs in heart failure

I. S. Varkholiak¹, B. V. Gutyj¹, D. F. Gufriy¹, R. M. Sachuk², R. V. Mylostyvyi³, M. L. Radzykhovskiy⁴,
H. M. Sedilo⁵, O. O. Izhboldina³

¹Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, Pekarska Str., 50, Lviv, 79010, Ukraine

²Rivne State University for the Humanities, Plastova Str., 29-a, Rivne, 33028, Ukraine

³Dnipro State Agrarian and Economic University, S. Efremov Str. 25, 49600, Dnipro, Ukraine

⁴National University of Life and Environmental Sciences of Ukraine, Heroyiv Oborony Str., 15, Kyiv, 03041, Ukraine

⁵Institute of Agriculture of Carpathian region of Ukraine, NAAS of Ukraine, Grushevskogo Str., 5, Obroshino, 81115, Ukraine

Article info

Received 06.09.2021

Received in revised form

07.10.2021

Accepted 08.10.2021

Correspondence author

Iryna Varkholiak

Tel.: +38-096-486-26-85

E-mail: irynekvet@ukr.net

2021 Varkholiak I. et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



Contents

1. Introduction	76
2. Materials and methods	77
3. Results and discussion	78
4. Conclusions	81
References	81

Abstract

The study aimed to investigate the effect of the drug “Bendamine” on dogs' clinical and morphological parameters in heart failure. Two groups of dogs were formed for research: control (healthy) and experimental (sick). The 30-day experiment included ten dogs from the control group, ten dogs of the observed (unhealthy) spaniel breed, and 10–12 years old dogs. The treatment regimen for sick dogs: furosemide was administered orally on an empty stomach at 2 mg/kg every 12 hours; enalapril was administered orally at 0.5 mg/kg every 12 hours; Bendamine was administered orally on an empty stomach at 20 mg/kg every 24 hours. It is recommended to divide the dose into two doses. In the study of hematopoiesis, we found that erythrocytes in dogs with heart failure increased by 18.2 %, while hemoglobin levels decreased by 1.8 %. Before treatment, red blood cell counts were found to reduce the mean hemoglobin in the erythrocyte and the mean erythrocyte volume. In the experimental group of dogs treated with the “Bendamine”, normalization of morphological blood parameters was found. The number of erythrocytes was 5.8 ± 0.06 T/L, and the hemoglobin level was 143.5 ± 4.7 g/L. The use of the drug “Bendamine” contributed to the gradual restoration of the functional state of the hematopoietic system in dogs with heart failure. This is also indicated by the red blood cell index of the dogs after the course of treatment. The therapy application in the experimental group significantly reduced the frequency and severity of shortness of breath and increased endurance during exercise. There was also a decrease in the frequency and duration of cough attacks. After treatment, signs, and intensity of ascites decreased in dogs of the experimental group. It has been suggested that this is due to an increase in myocardial contractile function due to the positive inotropic action of Bendamine. The owners also recorded an improvement in appetite in animals after 30 days of therapy. Even in the dogs of the experimental group, after treatment, physical activity and emotional reactions improved. They were less depressed and more inclined to communicate with the owners. Thus, the use of the cardiac drug “Bendamine” in dogs with heart failure positively affected the restoration of hematopoiesis and the normalization of morphological parameters of the blood.

Keywords: pharmacology, Bendamine, heart failure, cardiomyopathy, dogs.

Citation:

Varkholiak, I. S., Gutyj, B. V., Gufriy, D. F., Sachuk, R. M., Mylostyvyi, R. V., Radzykhovskiy, M. L., Sedilo, H. M., & Izhboldina, O. O. (2021). The effect of the drug “Bendamine” on the clinical and morphological parameters of dogs in heart failure. *Ukrainian Journal of Veterinary and Agricultural Sciences*, 4(3), 76–83.

1. Introduction

The results of research and summarizing the literature indicate that more than 10 % of domestic diseases account for the share of cardiovascular disease (Borgarelli et al., 2004; 2007; Borgarelli & Buchanan, 2012; Reynolds et al., 2012; Hollmer et al., 2017). It is worth noting that heart disease in pets is not always clinically manifested, so pet owners often learn about cardiovascular disease in their pets too late. When detecting cardiovascular pathology in animals, it is essential to establish the degree of hemodynamic

disorders, as well as diseases of other organs, which may be crucial for the course and prognosis (Cornell et al., 2004; Chetboul & Tissier, 2012; Fox, 2012; Lopez-Alvarez et al., 2015; Larouche-Lebel et al., 2019).

Experimental studies obtained in recent years indicate the urgency of developing drugs of complex action to prevent the development of cardiovascular disease in dogs. This requires a much deeper study of the pathogenesis of heart failure, including cardiomyopathy (Tilley et al., 2008; Merveille et al., 2015; Ramirez et al., 2016; Menciotti et al., 2017; Yata et al., 2019; Morgan et al., 2020).

Given the analysis of data from domestic and foreign researchers, the development of an easy-to-use and safe complex cardiac drug, the use of which will increase the effectiveness of treatment of animals and a wide range of cardiovascular pathologies, is on time (Undhad et al., 2012; Trofimjak & Slivinska, 2016; Zhulikova, 2016). In this aspect, it should be noted that the introduction of new cardiac drugs in the practice of veterinary medicine is exceptionally relevant and promising. Among the cardiopharmaceuticals in veterinary medicine, drugs based on pimobendan are of interest, as their action is to increase the contractile capacity of the heart and thus improve trophism. Due to positive inotropic and vasodilatory effects on the heart, failure pimobendan increases the strength of heart rate and reduces both preload and post-load (Oldach et al., 2019; Tjostheim et al., 2019; Varcholyak & Gutyj, 2019).

Given the positive effects of pimobendan on the body of animals in developing heart failure for the treatment and prevention of this pathology, it is necessary to use drugs containing the above active substance (Trofimiak & Slivinska, 2021).

According to some scientists, the primary pathogenetic changes in the formation of the pathology of the cardiovascular system are closely related to the overstrain of the mechanisms of the utilization of reactive oxygen species and the degree of disturbances in the system POL - AOC and are primarily determined by the immune system (Keene et al., 2019). Their imbalance underlies metabolic disorders in general, which significantly affects the state of cell membranes. In addition, among the metabolism indicators in the development of pathology, the system "Lipid peroxidation – Antioxidant protection system" is characterized by early deviations (Martyshuk & Gutyj, 2019; Nazaruk et al., 2021; Martyshuk & Hutyi, 2021). They play a leading role in adopting a healthy body to extreme conditions and the development of much deeper disorders of pathology (Martyshuk et al., 2016; 2018; 2019). In particular, it is considered proven that changes in the course of lipid peroxidation processes are one of the pathogenetic mechanisms of cardiovascular pathology (Varkholiak et al., 2020).

Violation of the antioxidant defense system of dogs under the influence of toxic substances and its correction with the use of various combinations of pharmacological and natural antioxidants is relevant and timely (Lavryshyn et al., 2016).

In veterinary medicine, one of the most promising drugs in the group of antioxidants are derivatives of 3-oxypyridine, in particular ethylmethylhydroxypyridine succinate – a direct-acting antioxidant. The mechanism of action of this drug is antioxidant and membrane-protective action (Varkholiak et al., 2020). It inhibits the processes of lipid peroxidation and promotes the activity of superoxide dismutase, which neutralizes the starting radical of free radical processes. Under conditions of tissue ischemia, this drug enhances the compensatory activation of aerobic glycolysis, reduces the degree of inhibition of oxidative processes in the Krebs cycle, and promotes the activation of ATP synthesis. Under the influence of ethylmethylhydroxypyridine succinate, a decrease in cardiomyocytes of a specific protein was found, which accelerates apoptosis. Transmembrane ionic currents are also modulated: slow current through calcium channels is slowed down, fast sodium channel blockade is averted, and the fast-activated potassium current component of delayed rectification (JKR) is

blocked (Varkholiak & Gutyj, 2018; 2019; Varkholiak et al., 2019; 2021).

Thus, ethylmethylhydroxypyridine succinate has a complex effect on the metabolism of the myocardium of animals.

A combined approach to treating animals with heart failure, which is based on the use of phosphodiesterase-3 inhibitors and antioxidants, is relevant. Because antioxidant compounds can protect healthy cells and tissues of dogs from the development of unwanted side effects caused by the development of heart failure. In addition, it is known that the development of this pathology is characterized by oxidative stress, which causes a particular metabolic activity of antioxidants (Martyshuk, 2016; Varkholiak & Gutyj, 2019).

Thus, the use of antioxidants in the heart for heart failure in dogs can improve the redox adaptation of heart muscle cells and protect them from the harmful effects of free radicals.

The **study aimed** to investigate the effect of the drug "Bendamine" on dogs' clinical and morphological parameters in heart failure.

2. Materials and methods

Two groups of dogs were formed for research: control (healthy) and experimental (sick). The 30-day experiment included ten dogs of the control group and ten dogs of the experimental (sick) breed of spaniel and dogs 10–12 years old.

During the period 2016–2019, 567 dogs were clinically studied. The animals underwent non-invasive research methods (echocardiography, electrocardiography, chest X-ray) and hematological and biochemical blood tests. Heart disease was detected in 339 animals. Among the breeds of dogs used, "Bendamine" there were taxis (23 animals), dogs (48 animals), cocker spaniels (92), Yorkshire terriers (108), Pekingese (18), Labradors (15), Labradors (15), Golden Retrievers (1), German Shepherds (7), Doberman Pinschers (2), Staffordshire Bull Terriers (4), mestizos and other breeds (21).

The treatment regimen for sick dogs: furosemide was administered orally on an empty stomach at 2 mg/kg every 12 hours; enalapril was administered orally at 0.5 mg/kg every 12 hours; bendamine was administered orally on an empty stomach at 20 mg/kg every 24 hours. It is recommended to divide the dose into two doses.

The following parameters were determined in heparin-stabilized blood: the number of erythrocytes was photoelectrocolometrically according to the method of E. S. Gavrilets et al. (1966); the number of leukocytes – with the help of Goryaev's grid in the counting chamber; hemoglobin content – by the method of L. M. Pimenova et al. (1975). The hematocrit value was determined by the micro method in the modification of Todorov J. According to the formulas, blood indices were mathematically calculated according to the number of erythrocytes, blood hemoglobin content, and hematocrit content. The leukogram was determined by morphological parameters of the number of white blood cells with differentiated counting of different forms of leukocytes (Vlizlo et al., 2012).

All animal manipulations were carried out following the European Convention for the Protection of Vertebrate Ani-

mals Used for Experimental and Scientific Purposes (Strasbourg, 1986).

The analysis of research results was performed using the software package Statistica 6.0. Student's t-test assessed the probability of differences. The results were considered plausible at $P \leq 0.05$.

3. Results and discussion

When determining the dynamics of the incidence of dogs with cardiovascular pathology based on the analysis of journal reports in veterinary clinics of Lviv, it was found that in the period 2016–2019, this pathology was manifested in 7.8–12.7 % of surveyed animals, with less than half of the cases, were diagnosed with chronic heart failure (5.3–8.1 % of the examined animals). The disease had no seasonal dynamics. The development of heart failure in dogs was accompanied by various clinical symptoms depending on the stage of the process. Initially, most owners observed an increase in the frequency of respiratory movements during

sleep, then – a decrease in endurance during walks, shortness of breath, and cough. With the development of the pathological process, there was pulmonary edema (recorded in one dog), then – ascites. Decreased myocardial contractility, blood stasis, and hemodynamic disturbances lead to the development of hypoxia, so in sick animals, there was a decrease in the rate of filling the capillaries of mucous membranes, pallor, cyanosis. Body temperature in sick animals was within physiological parameters, while heart rate and respiration were increased compared to healthy dogs due to the activation of compensatory mechanisms.

Monitoring the frequency of respiratory movements in dogs during sleep is a relatively new indicator used in clinical practice. Raising the CDR with high specificity and sensitivity can predict the likelihood of pulmonary edema, assess the effectiveness of diuretic therapy in congestive heart failure, select the minimum effective dose of diuretic, predict the onset of decompensation, and timely adjust the treatment regimen.

Table 1

Indicators of the frequency of respiratory movements of dogs with the development of heart failure and the action of the drug “Bendamine” ($M \pm m$; $n = 10$)

Indicators	Group of animals		
	Control	Research	
		Before treatment	After treatment
Frequency of respiratory movements for 1 min in a state of sleep	12–20	30–58	20–35

The therapy application in the experimental group significantly reduced the frequency and severity of shortness of breath and increased endurance during exercise. There was also a decrease in the frequency and duration of cough attacks.

After treatment, signs, and intensity of ascites decreased in dogs of the experimental group. It has been suggested that this is due to an increase in myocardial contractile function due to the positive inotropic action of bendamine.

The owners also recorded an improvement in appetite in animals after 30 days of therapy. Even in the dogs of the experimental group, after treatment, physical activity and emotional reactions improved. They were less depressed and more inclined to communicate with the owners.

A decrease in cardiac coefficients was found during radiography in the experimental group after the therapy application (Table 2). An electrocardiographic study showed a reduction in heart rate in 10 dogs, which may be due to the negative chronotropic effect of the drug, which is characteristic of the group of phosphoesterases. The decrease in heart rate, in turn, is due to peripheral dilatation, which is achieved by inhibiting phosphoesterase III. In six dogs out of ten, ventricular ectopic contractions were detected, the diversity of which was 18–40 for 20 min and was reduced to 10–27, respectively, on day 30 of the recommended therapy (Fig. 1).

Table 2

Radiographic parameters in dogs with the development of heart failure and the action of the drug “Bendamine” ($M \pm m$; $n = 10$)

Indicators	Group of animals		
	Control	Research	
		Before treatment	After treatment
B'jukenen coefficient	≤ 10.5	11.1–13.3	10.4–11.2
Cardiothoracic index	up to 0.55	0.55–0.67	0.55–0.63
VLAS	2.1	2.3–3.8	2.3–2.5



Fig. 1. Electrocardiography of the heart of a spaniel dog. Ectopic contraction. Supraventricular extrasystole

Echocardiographic examination of all dogs showed an increase in the ratio of LP/Ao, which indicates the presence of a tria dilation, which is characteristic of patients with this stage of heart failure. After treatment, there was a slight decrease in the ratio of LP/Ao. The positive effect of the drug is associated with increased myocardial contractile function and decreased postload (positive inotropic and vasodilating effect of bendamine). After all, a decrease in pressure in the left ventricle leads to a decrease in pressure in the left atrium and pulmonary veins.

The index of left ventricular contractility increased in the experimental group after treatment, which correlates with data on the pharmacodynamic properties of the drug (Fig. 2 and 3).

Thus, echocardiographic changes in treated dogs were manifested by an increase in left ventricular systolic function and a decrease in left atriodilation.

In treating dogs with heart failure, we used the cardiac drug "Bendamine", which was fed to animals for 30 days. It was found that before treatment, the number of erythrocytes in the blood of dogs with clinical signs of heart failure was higher by 18.2 %, while the hemoglobin level was lower by 1.8 % compared to the control group of dogs.

After the course of treatment, it was found that in the blood of dogs of the experimental group, the number of erythrocytes and hemoglobin levels ranged between 5.8 ± 0.06 T/L and 143.5 ± 4.7 g/L, respectively (Table 3).

It was also found that the hematocrit value in the control group of dogs ranged from 0.43 ± 0.04 L/L, while in the experimental group of dogs with clinical signs of heart failure, it decreased by 11.6 %. On the 30th day of the experiment, after a course of treatment and use of the drug "Bendamine" in the blood of the experimental group of dogs found, an increase in hematocrit by 26.3 % compared with the blood taken before treatment of animals.

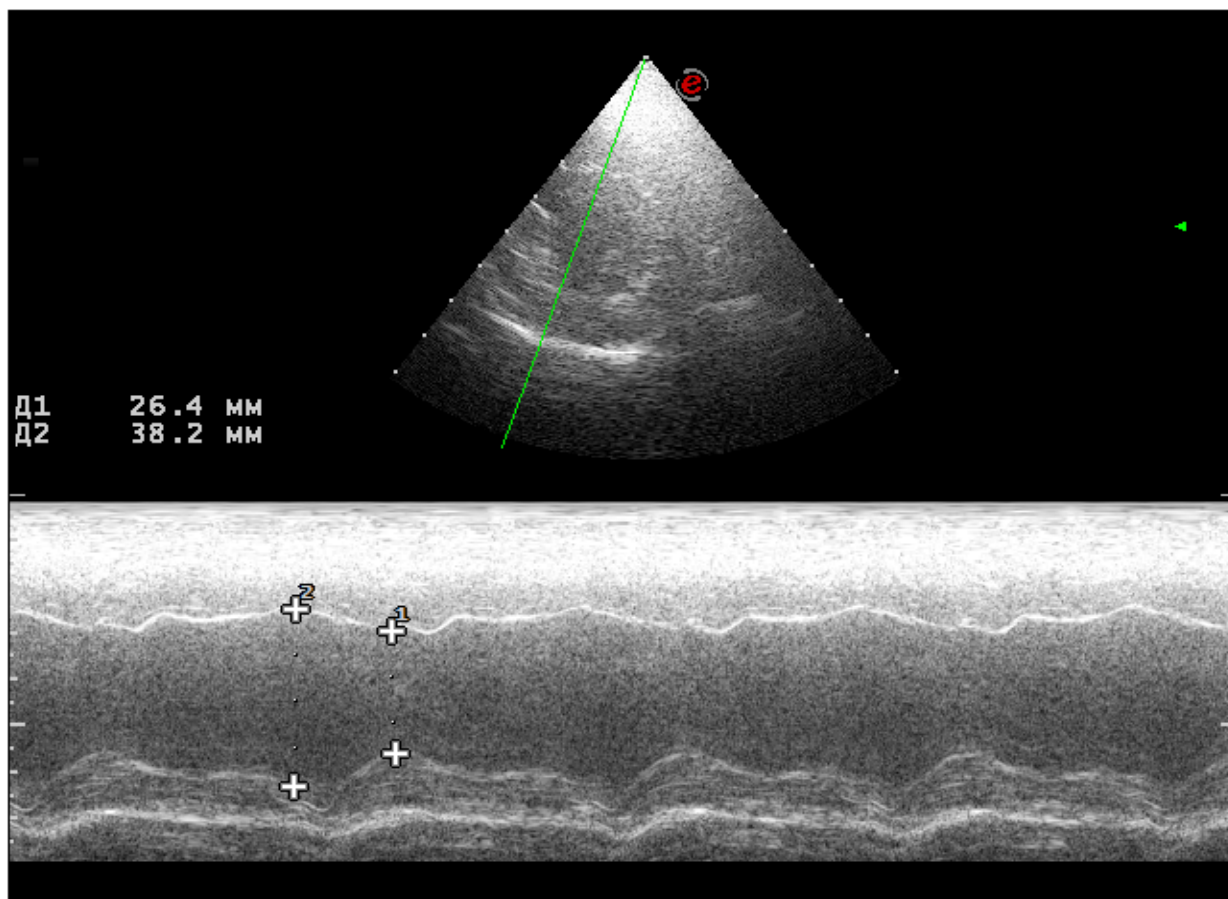


Fig. 2. Ultrasonogram of the dog's heart before therapy, M-mode. R1 is the final systolic size, and R2 is the final diastolic size. FS-32 %, PV-60 %

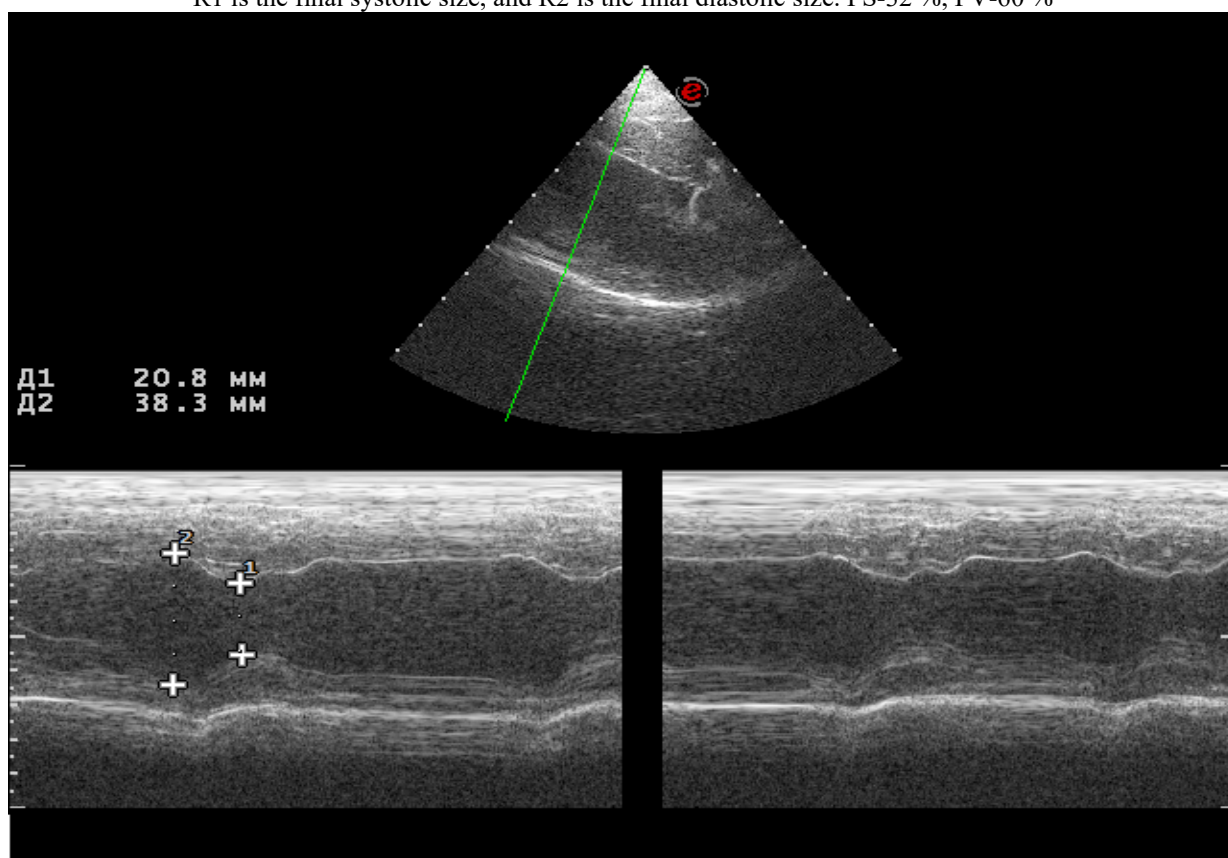


Fig. 3. Ultrasonogram of the dog's heart after 30 days of therapy, M-mode. D1 is the final systolic size, and R2 is the final diastolic size. FS-47 %, PV-79 %

Table 3

Hematological parameters of the blood of dogs with heart failure and the action of the drug “Bendammine” (M ± m; n = 10)

Indicators	Group of animals		
	Control	Research	
		Before treatment	After treatment
Erythrocytes, T/L	5.5 ± 0.05	6.5 ± 0.07***	5.8 ± 0.06*
Hemoglobin (g/L)	130.4 ± 5.1	128.1 ± 4.4	143.5 ± 4.7*
Hematocrit, l/L	0.43 ± 0.04	0.38 ± 0.06*	0.48 ± 0.06
The average content of hemoglobin in the erythrocyte, pg	23.7 ± 0.65	19.7 ± 0.74***	24.7 ± 0.69
Mean erythrocyte volume, μm ³	78.2 ± 3.4	58.4 ± 3.6***	82.7 ± 4.0
The average concentration of hemoglobin in erythrocytes, g/100 ml	30.3 ± 0.58	33.7 ± 0.47***	29.8 ± 0.50

When determining red blood cell indices in dogs of the control group, it was found that the average hemoglobin content in one erythrocyte was 23.7 ± 0.65 pg, the average concentration of hemoglobin in erythrocytes ranged from 30.3 ± 0.58 g/100 ml. In contrast, the average erythrocyte volume was 78.2 ± 3.4 μm³. In patients of dogs of the experimental group, red blood cell index values probably changed, namely: the average erythrocyte volume and the average hemoglobin content in one erythrocyte probably decreased by 25.3 and 16.9 %, while the average hemoglobin concentration in erythrocytes probably increased by 11.2 % relative to the control group of dogs.

After a course of treatment for dogs with heart failure, it was found that on the 30th day of the experiment, the indicators of red blood cell indices of the experimental group of dogs fluctuated within physiological limits.

When determining the number of leukocytes in the blood of dogs with heart failure, we found a slight increase throughout the experiment, were at the beginning of the investigation, they increased by 5.5 %, and on the 30th day of treatment – by 7.7 % compared with the control group (Table 4).

Table 4

Blood leukogram of dogs with heart failure and the action of the drug “Bendammine” (M ± m; n = 10)

Indicators	Group of animals		
	Control	Research	
		Before treatment	After treatment
Leukocytes, G/L	9.1 ± 0.3	9.6 ± 0.4	9.8 ± 0.3
Eosinophils, %	5.0 ± 0.6	2.4 ± 0.4**	3.0 ± 0.4*
Neutrophils rod-shaped, %	4.0 ± 0.3	6.3 ± 0.2***	5.1 ± 0.3*
Segmental neutrophils, %	55.8 ± 5.3	72.1 ± 6.0*	65.3 ± 5.5
Lymphocytes, %	22.3 ± 3.1	10.4 ± 2.5**	15.3 ± 2.9
Monocytes, %	4.6 ± 0.7	6.1 ± 0.6	5.1 ± 0.8

A low percentage of eosinophils and lymphocytes was found in the blood of dogs with heart failure, where they decreased by 2.6 and 11.9 % compared to the control group. The percentage of neutrophils in the blood of dogs in the experimental group increased. For example, the rate of rod-shaped neutrophils increased by 2.3 %, while the segment of nuclear - increased by 16.3 %, respectively.

The analysis of the leukogram of sick animals of the experimental group showed an increase in the percentage of monocytes to 6.1 ± 0.6 %, while after treatment, this figure was 5.1 ± 0.8 %.

During the treatment period, a relatively good prognostic indicator is an increase in the percentage of lymphocytes in the blood to 15.3 ± 2.9 % and eosinophils to 3.0 ± 0.4 %.

After treatment in the blood of the experimental group of dogs on the 30th day of the experiment, the percentage of both segmental and rod-shaped neutrophils, compared to the period before treatment, decreased by 6.8 and 1.2 %, respectively.

4. Conclusions

Studies confirm the feasibility of using the drug “Bendammine” in dogs with the development of heart failure. The use of the cardiac drug “Bendammine” in dogs with heart

failure positively affected the restoration of hematopoiesis and the normalization of morphological parameters of the blood.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Borgarelli, M., & Buchanan, J. W. (2012). Historical review, epidemiology, and natural history of degenerative mitral valve disease. *Journal of Veterinary Cardiology*, 14(1), 93–101. DOI: 10.1016/j.jvc.2012.01.011.
- Borgarelli, M., Tarducci, A., Zanatta, R., & Haggstrom, J. (2007). Decreased systolic function and inadequate hypertrophy in large and small breed dogs with chronic mitral valve insufficiency. *Journal of Veterinary Internal Medicine*, 21(1), 61–67. DOI: 10.1892/0891-6640(2007)21[61:dsfaih]2.0.co;2.
- Borgarelli, M., Zini, E., D'Agnolo, G., Tarducci, A., Santilli, R. A., Chiavegato, D., Tursi, M., Prunotto, M., & Häggström, J. (2004). Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. *Journal of Veterinary Cardiology*, 6(2), 27–34. DOI: 10.1016/S1760-2734(06)70055-8.
- Chetboul, V., & Tissier, R. (2012). Echocardiographic assessment of canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*, 14(1), 127–148. DOI: 10.1016/j.jvc.2011.11.005.

- Cornell, C. C., Kittleson, M. D., Torre, P. D., Haggstrom, J., Lombard, C. W., Pedersen, H. D., Vollmar, A., & Wey, A. (2004). Allometric scaling of M-mode cardiac measurements in normal adult dogs. *Journal of Veterinary Internal Medicine*, 18(3), 311–321. DOI: 10.1892/0891-6640(2004)18<311:asomcm>2.0.co;2.
- Fox, P. R. (2012). Pathology of myxomatous mitral valve disease in the dog. *Journal of Veterinary Cardiology*, 14(1), 103–126. DOI: 10.1016/j.jvc.2012.02.001.
- Hollmer, M., Willesen, J. L., Tolver, A., & Koch, J. (2017). Left atrial volume and function in dogs with naturally occurring myxomatous mitral valve disease. *Journal of Veterinary Cardiology*, 19(1), 24–34. DOI: 10.1016/j.jvc.2016.08.006.
- Keene, B. W., Atkins, C. A., Bonagura, J. D., Fox, P. R., Häggström, J., Fuentes, V. L., Oyama, M. A., Rush, J. E., Stepien, R., & Uechi, M. (2019). ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *Journal of Veterinary Internal Medicine*, 33(3), 1127–1140. DOI: 10.1111/jvim.15488.
- Larouche-Lebel, E., Loughran, K. A., & Oyama, M. A. (2019). Echocardiographic indices and severity of mitral regurgitation in dogs with preclinical degenerative mitral valve disease. *Journal of Veterinary Internal Medicine*, 33(2), 489–498. DOI: 10.1111/jvim.15461.
- Lavryshyn, Y. Y., Varkholyak, I. S., Martyschuk, T. V., Guta, Z. A., Ivankiv, L. B., Paladischuk, O. R., Murska, S. D., Gutyj, B. V., & Gufriy, D. F. (2016). The biological significance of the antioxidant defense system of animals body. *Scientific Messenger LNUVMBT named after S.Z. Gzhytskyj*, 18, 2(66), 100–111. DOI: 10.15421/nlvvet6622.
- Lopez-Alvarez, J., Elliott, J., Pfeiffer, D., Chang, Y.-M., Mattin, M., Moonarmart, W., Hezzell, M.J., & Boswood, A. (2015). Clinical Severity Score System in Dogs with Degenerative Mitral Valve Disease. *Journal of Veterinary Internal Medicine*, 29(2), 575–581. DOI: 10.1111/jvim.12544.
- Martyschuk, T. V. (2016). The influence of oxidative stress on the state of the antioxidant defense system in the organism of rats. *Regulatory Mechanisms in Biosystems*, 7(1), 8–12. DOI: 10.15421/021602.
- Martyschuk, T. V., & Hutyi, B. V. (2021). Imunofiziologichniy stan ta antyoksydantnyi potentsial orhanizmu porosiat za umov oksydatyinoho stresu ta dii koryhuiuchykh chynnykiv: monohrafiia. Lviv: SPOLOM (in Ukrainian).
- Martyschuk, T. V., Gutyj, B. V., & Vishchur, O. I. (2016). Level of lipid peroxidation products in the blood of rats under the influence of oxidative stress and under the action of liposomal preparation of “Butaselvevit”. *Biological Bulletin of Bogdan Khmelnytsky Melitopol State Pedagogical University*, 6(2), 22–27. DOI: 10.15421/201631.
- Martyschuk, T. V., Gutyj, B. V., & Vishchur, O. I. (2018). Indicators of functional and antioxidant liver status of rats under oxidative stress conditions and on the action of the liposomal drug “Butaselvevit”. *Scientific Messenger of Lviv National University of Veterinary Medicine and Biotechnologies*, 20(89), 100–107. DOI: 10.32718/nlvvet8919.
- Martyschuk, T. V., Gutyj, B. V., Vishchur, O. I., & Todoriuk, V. B. (2019). Biochemical indices of piglets blood under the action of feed additive “Butaselvevit-plus”. *Ukrainian Journal of Veterinary and Agricultural Sciences*, 2(2), 27–30. DOI: 10.32718/ujvas2-2.06.
- Martyschuk, T., & Gutyj, B. (2019). Influence of feed additive “Butaselvevit-Plus” on antioxidant status of rats in conditions of oxidative stress. *Scientific Messenger of LNU of Veterinary Medicine and Biotechnologies. Series: Agricultural Sciences*, 21(90), 76–81. DOI: 10.32718/nlvvet-a9013.
- Menciotti, G., Borgarelli, M., Aherne, M., Wesselowski, S., Haggstrom, J., Ljungvall, I., Lahmers, S. M., & Abbott, J. A. (2017). Mitral valve morphology assessed by three-dimensional transthoracic echocardiography in healthy dogs and dogs with myxomatous mitral valve disease. *Journal of Veterinary Cardiology*, 19(2), 113–123. DOI: 10.1016/j.jvc.2017.01.002.
- Merveille, A.-C., Bolen, G., Krafft, E., Roels, E., Gomart, S., Etienne, A.-L., Clercx, C., & Entee, K. Mc. (2015). Pulmonary Vein-to-Pulmonary Artery Ratio is an Echocardiographic Index of Congestive Heart Failure in Dogs with Degenerative Mitral Valve Disease. *Journal of Veterinary Internal Medicine*, 29(6), 1502–1509. DOI: 10.1111/jvim.13634.
- Morgan, K. R. S., Monteith, G., Raheb, S., Colpitts, M., & Fonfara, S. (2020). Echocardiographic parameters for the assessment of congestive heart failure in dogs with myxomatous mitral valve disease and moderate to severe mitral regurgitation. *The Veterinary Journal*, 263, 1–25. DOI: 10.1016/j.tvjl.2020.105518.
- Nazaruk, N. V., Gutyj, B. V., Gufriy, D. F., Leskiv, Kh. Ya., Ivashkiv, R. M., & Martyschuk, T. V. (2021). The effect of methyphen and Vitamix se on the level of products of bull lipid peroxide oxidation under nitrate-cadmium load. *Colloquium-journal*, 7(94), 16–18. DOI: 10.24412/2520-6990-2021-794-16-18
- Oldach, M. S., Ueda, Y., Ontiveros, E. S., Fousse, S. L., Harris, S. P., & Stern, J. A. (2019). Cardiac Effects of a Single Dose of Pimobendan in Cats With Hypertrophic Cardiomyopathy; A Randomized, Placebo-Controlled, Crossover Study. *Front Vet Sci*, 6, 15. DOI: 10.3389/fvets.2019.00015.
- Ramirez, V. L., Berrío, A., & Arias, M. P. (2016). Correlation between the clinical stage, echocardiographic findings and systemic blood pressure in dogs with Degenerative Disease of the Mitral Valve. *CES Veterinary medicine and Zootechnics*, 11(2), 61–72. DOI: 10.21615/cesmvz.11.2.5.
- Reynolds, C. A., Brown, D. C., Rush, J. E., Fox, P. R., Nguyenba, T. P., Lehmkuhl, L. B., Gordon, S. G., Kellihan, H. B., Stepien, R. L., Lefbom, B. K., Meier, C. K., & Oyama, M. A. (2012). Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: *The PREDICT cohort study*. *Journal of Veterinary Cardiology*, 14(1), 193–202. DOI: 10.1016/j.jvc.2012.01.008.
- Tilley, P. L., Francis, W. K., Smith, J., Oyama, M.A. (2008). *Manual of canine and feline cardiology*. Copyright by Saunders, an imprint of Elsevier Inc, 105–106 (Fourth edition).
- Tjostheim, S. S., Kellihan, H. B., Grint, K. A., & Stepien, R. L. (2019). Effect of sildenafil and pimobendan on intracardiac heartworm infections in four dogs. *J Vet Cardiol.*, 23, 96–103. DOI: 10.1016/j.jvc.2019.02.001.
- Trofimiak, R., & Slivinska, L. (2021). Diagnostic value of echocardiographic indices of left atrial and ventricular morphology in dogs with myxomatous mitral valve disease (MMVD). *Ukrainian Journal of Veterinary and Agricultural Sciences*, 4(1), 16–23. DOI: 10.32718/ujvas4-1.04.
- Trofimjak, R., & Slivinska, L. (2016). Diagnosis of chronic heart failure dogs – existing methods and future prospects. *Scientific Messenger of LNU of Veterinary Medicine and Biotechnologies. Series: Veterinary Sciences*, 18(71), 130–133. DOI: 10.15421/nlvvet7129.
- Undhad, V. V., Fefar, D. T., Jivani, B. M., Gupta, H., Ghodasara, D. J., Joshi, B. P. & Prajapati, K. S. (2012). Cardiac troponin: an emerging cardiac biomarker in animal health. *Vet. World*, 5, 508–511. DOI: 10.5455/vetworld.2012.508-511.
- Varcholyak, I. S., & Gutyi, B. V. (2019). Determination of the chronic toxicity of preparation “Bendamin” on laboratory animals. *Theoretical and Applied Veterinary Medicine*, 7(2), 63–68. DOI: 10.32819/2019.71011.
- Varkholiak, I. S., & Gutyj, B. V. (2018). Determination of acute toxicity of “Bendamin” drug in laboratory animals. *Scientific Messenger of Lviv National University of Veterinary Medicine and Biotechnologies*, 20(92), 209–212. DOI: 10.32718/nlvvet9243.
- Varkholiak, I. S., & Gutyj, B. V. (2019). The degree of cumulation of the “Bendamin” drug in the body of white rats. *Scientific Messenger of Lviv National University of Veterinary Medicine and Biotechnologies. Series: Veterinary Sciences*, 21(94), 82–85. DOI: 10.32718/nlvvet9415.
- Varkholiak, I. S., Gutyj, B. V., Leskiv, Kh. Ya., Kushnir, V. I., Hariv, I. I., Martyschuk, T. V., & Guta, Z. A. (2021). The effect of bendamine on antioxidant protection of rats' myocardium in

- doxorubicin intoxication. *Colloquium-journal*, 7(94), 18–21. DOI: 10.24412/2520-6990-2021-794-18-21
- Varkholiak, I. S., Gutyj, B. V., Leskiv, Kh. Ya., Kushnir, V. I., Hariv, I. I., Martyshuk, T. V., & Guta, Z. A. (2021). The effect of bendamine on antioxidant protection of rats' myocardium in doxorubicin intoxication. *Colloquium-journal*, 7(94), 18–21. DOI: 10.24412/2520-6990-2021-794-18-21.
- Varkholiak, I., Gutyj, B., & Leskiv, Kh. (2020). Influence of “Bendamin” on the indices of antioxidant protection in rat’s blood by an experimental doxorubicin-induced cardiomyopathy. *Scientific Light*, 35, 41–44.
- Varkholiak, I., Gutyj, B., Kushnir, V., Nazaruk, N., Lisnyak, O., & Yurynets, T. (2020). The effect of bendamine on the intensity of lipid peroxidation and the activity of the antioxidant defense system of blood in rats in experimental doxorubicin-induced cardiomyopathy. *Scientific Messenger of LNU of Veterinary Medicine and Biotechnologies. Series: Veterinary Sciences*, 22(100), 36–40. DOI: 10.32718/nvlvet10007.
- Vlizlo, V. V., Fedoruk, R. S., & Raty`ch, I. B. (2012). Laboratorni metody` doslidzhen` u biologiyi, tvary`nny`cztyvi ta veterinary`narnij medy`cy`ni: dovidny`k. L`viv: Spolom (in Ukrainian).
- Yata, M., Kooistra, H. S., & Beijerink, N. J. (2019). Cardiorenal and endocrine effects of synthetic canine BNP1-32 in dogs with compensated congestive heart failure caused by myxomatous mitral valve disease. *J Vet Intern Med.*, 33(2), 462–470. DOI: 10.1111/jvim.15416.
- Zhulikova, O. A. (2016). Monitoring rasprostraneniya serdechno-sosudistyh zabolevanij sredi koshek i sobak v g. Blagoveshhensk amurskoj oblasti. *Dal'nevostochnyj agrarnyj vestnik*, 2(38), 49–56. <https://cyberleninka.ru/article/n/monitoring-rasprostraneniya-serdechno-sosudistyh-zabolevanij-sredi-koshek-i-sobak-v-g-blagoveschensk-amurskoy-oblasti> (in Russian).