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STUDIES REGARDING THE OPTIMIZATION OF THE THERAPEUTICAL MANAGEMENT IN CANINE BABESIOSIS

STUDII PRIVIND OPTIMIZAREA MANAGEMENTULUI TERAPEUTIC ÎN BABESIOZA CANINĂ

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ABSTRACT

The study regarding the optimization of the therapeutic management in babesiosis in dogs consisted in using of three therapeutic schemes, namely: single dose (6.6 mg/kg) of Imizol (imidocarb), administered subcutaneously; half dose of Imizol recommended by the manufacturer (3.3 mg/kg), together with a treatment with clindamycin at a dose of 30 mg/kg at 12 hours, for 5 days, then 30 mg/kg at 24 hours, for the further 16 days; and a treatment with only clindamycin in the doses mentioned above. The efficacy of the medicinal products used in different doses and combinations for each of the three therapeutic schemes, was demonstrated by remission of the anaemia and recovery of the haemoglobin load. Thus, 12 days after the initiation of the specific treatment, in the case of majority of the patients we observed a distinctly significant increase ($p<0.01$) of the mean values of the red blood cells, and a statistically significant increase ($p<0.05$) of the average values of haemoglobin and haematocrit. Also, all the parameters that attest the morphofunctional integrity of the liver and the nephron, evaluated at 12 days after the beginning of the treatment, returned to normal, falling within the characteristic limits of the species.

Key words: babesiosis, dogs, haematological and biochemical exams, therapeutic management

REZUMAT

Studiul privind optimizarea managementului terapeutic în babesioză la câine, a constat în folosirea a trei scheme terapeutice, și anume: doză unică (6,6 mg/kg) de Imizol (imidocarb), administrat subcutanat; jumătate de doză de Imizol recomandată de producător (3,3 mg/kg), alături de un tratament cu clindamicină în doză de 30 mg/kg la 12 ore, timp de 5 zile, după care 30 mg/kg la 24 ore, timp de încă 16 zile; și tratamentul doar cu clindamicină în dozele amintite mai sus.

Eficacitatea produselor medicamentoase folosite în doze și combinații diferite în cele trei scheme terapeutice, a fost demonstrată prin remiterea anemiei și refacerea încărcăturii de hemoglobină. Astfel, la 12 zile de la inițierea tratamentului specific, la majoritatea pacienților se observă o creștere distinct semnificativă ($p<0,01$) a valorilor medii ale hematiilor și o creștere semnificativă din punct de vedere statistic ($p<0,05$) a valorilor medii ale hemoglobinei și hematocritului. De asemenea, toți parametrii care atestă integritatea morfofuncțională a ficatului și nefronului, determinați la 12 zile de la începerea tratamentului, au revenit și ei la normal, încadrându-se în limitele caracteristice speciei.

Cuvinte cheie: babesioză, câine, analize biochimice și hematologice, management terapeutic

Due to the two factors involved, the host organism (of different breeds and ages, at which different collateral conditions may or may not be present) and the parasite (of different species, three identified in Romania), babesiosis develops and expresses a highly complex and intricate clinical-pathogenical and paraclinical ensemble (2, 3, 5, 10).

The purpose of this paper is to contribute to the identification and integrated assessment of the epidemiological framework and coordinates of babesiosis on a delimited area in Ilfov County. At the same time, it aims to evaluate and subsequently appreciate in an integrated manner the prognostic values of the variations of some haematological and biochemical parameters and last but not least, to compare the therapeutic efficacy of the various medicinal products used in the treatment of this parasitic disease in dogs.

The treatment in babesiosis in dogs, especially in the severe forms, is long-lasting, difficult, complex, and quite expensive, because it consists in establishing a specific medication, associated with a supportive treatment and even blood transfusion, where the case. In this context, the specific chemotherapy has

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the role of both prevention and treatment. Worth mentioning is the fact that the success of the treatment, respectively, its efficacy in babesiosis, most often depends on the early diagnosis of the disease and the prompt administration of the medication based on a correct therapeutic protocol. In our country, the most used pharmaceutical products for the treatment of dog babesiosis are: a chemotherapy drug - imidocarb dipropionate and some antimicrobials - clindamycin and sometimes doxycycline (9).

Taking into consideration these pathogenic coordinates, of overwhelming importance for the veterinary clinician, it can be considered of high importance the correct and complex approach of the evolution, in correlation with the active screening, for the clinical recovery of the patient and the removal of the causal agent, coordinates that are seen as defining milestones in the clinical and therapeutic management of this condition in dogs (8).

MATERIALS AND METHODS

The present study was performed from 2016 until 2018, on a number of 67 dogs belonging to several breeds, of different ages and genders. All dogs lived in Bucharest-Ilfov area, Romania.

It is worth mentioning the fact that, due to the quite large variations of the haematological and biochemical parameters that exist between different breeds of dogs, for the accuracy of the results and for a more accurate statistical interpretation, the patients in the control group were selected in such a manner that, they would largely belong to the same breeds as the patients with babesiosis.

The dogs in the group suspected of babesiosis, underwent rigorous physical and clinical examination. During the clinical examination, in most of the infested dogs (and included in the studied group), the presence of ticks could be observed on the skin.

Since the identification of the endoglobular parasites in the blood smear represents the decisive element of the etiological diagnosis, the infested dogs were included in the studied group after at least two peripheral blood smears (*May-Grunwald stain*) were performed in order to detect the *Babesia spp.* parasites from the red blood cells.

In order to confirm the diagnosis and establish an individualized therapeutic protocol in patients with suspicion of babesiosis, we resorted to harvesting biological samples (whole blood on EDTA) for haematological examination, to determine the degree of anaemia and biochemical exams, to determine the degree of impairment of the hepatic and renal functions. Methods and equipment used for haematological and biochemical exams have been described previously (6, 7).

Anamnestic data and disease history are an important component in the preparation and implementation of the protocol and the clinical examination chart, which is why the elements that are revealed from the (detailed) anamnesis may highlight various pre-existing or competitive conditions, as well as the clinical signs, but also the reason for presentation at the consult and medical evaluation (8, 11).

Imidocarb (Imizole) is the main babesicide used in dogs for prophylaxis and treatment of babesiosis (12, 13). It acts quickly because it destroys the parasites in a very short period of time (24-96 hours after administration). This medicine is administered to the dog in general, subcutaneously, (rarely intramuscularly) and very rarely intravenously due to its high toxicity (due to some cholinergic effects, manifested by hypersalivation, vomiting, sudden hypotension etc.) that can cause death within minutes. For this reason, the active substance falls into the category of drugs with low therapeutic index (TI<3), where the therapeutic dose equals the toxic dose.

RESULTS AND DISCUSSIONS

The recommended treatment for the patients with babesiosis in the studied group was, firstly, specific, as it was aimed at the use of some medicinal substances that will destroy the parasites, and secondly, symptomatic by the use of antianemia drugs, liver protectors, cardiotonic substances, glucose serum, antiemetic drugs, depending on the condition of the patients (12).

In this context, the priority objectives of the therapeutic conduct consisted in the correction of the humoral imbalances induced by the renal and hepatic insufficiency,and the stabilization of the patient consisted of intravenous fluid therapy (Ringer's Lactate solution, in dose of 50 ml/kg, Dextran 70 in dose of 10 ml/kg).

It is worth mentioning the fact that, in most cases, the therapeutic efficacy depended on the time of the clinical intervention, the degree of infestation and last but not least on the patient's age (1). Thus, in the patients with babesiosis from the studied group, together with the personalized symptomatic treatment for each case, we used 3 therapeutic schemes according to the degree of infestation (Table 1).

In the treatment of babesiosis, we used Imidocarb dipropionate (Imizol), as it is the most widely used

Table 1

Types of therapeutic protocol used in order to combat babesiosis in the patients from the studied group

Specification	THERAPEUTIC PROTOCOL		
	1	2	3
Category	CHEMOTHERAPEUTIC DRUG	ANTIMICROBIAL SUBSTANCES	CHEMOTHERAPEUTIC DRUG + ANTIMICROBIAL SUBSTANCES
Medicinal product	**IMIZOL** (imidocarb dipropionate)	**CLINDAMYCIN**	**IMIZOL + CLINDAMYCIN**
Dose	6,6 mg/kg single dose	30 mg/kg at 12 hours, for 5 days; then 30 mg/kg at 24 hours, for another 16 days	3,3 mg/kg - single dose + 30 mg/kg at 12 hours, for 5 days; then 30 mg/kg at 24 hours, for another 16 days
Number of patients *(n=19)*	**n=7** *(36.8%)*	**n=7** *(36.8%)*	**n=5** *(26.3%)*

drug in the treatment of babesiosis in dogs, demonstrating a high efficacy against the species of *Babesia canis*, at a single dose administered intramuscularly or subcutaneously (4). Although the mechanism of action of imidocarb dipropionate is little known, it is assumed that the imidocarb acts directly on the parasite, changing its size, number of nuclei and structure of the cytoplasm (vacuolization).

The other therapeutic protocol consisted in the use of clindamycin, which is an antibiotic from the lincosamides class, derived from lincomycin, considered by some authors to be a superior treatment alternative in terms of safety compared to imizol treatment because it has remarkable efficacy, increasing the body's immune response (12). The efficacy of the treatment (depending on the therapeutic protocol), was established by resorting to the haematological and biochemical examinations at different set time intervals.

Thus, the results of the haematological and biochemical examinations of the patients with babesiosis are presented below, 12 days after the start of the specific treatment (together with a symptomatic treatment, depending on each individual case).

Based on the obtained results, the average value of each determined parameter was calculated,after which a comparative statistical analysis was performed, before and after the treatment (Table 2). Following the comparative analysis of the variation of some haematological and biochemical parameters in the studied group of dogs with babesiosis, before and after the specific treatment, some differences with statistical significance can be observed and are mentioned below.

In this context, it can be mentioned that at 12 days after the administration of the specific treatment, depending on the clinical particularities of the patient, corroborated with other factors (e.g., age, sex, degree of infestation), haematological and biochemical parameters determined, return, in general, to normal, along with the deletion of the specific symptomatology and the stabilization of the patient. Thus, a distinctly significant increase ($p < 0.01$) of the mean values of the red blood cells (6.1 ± 0.8 mil./mm^3 of blood) can

Table 2

Variation of the mean values of some haematological and biochemical parameters, before and after treatment in the studied group of dogs with babesiosis

No.	PARAMETERS	The mean values of the control group *(n=13)*	The mean values of the patients with babesiosis *(n=19)*	The mean values after 12 days of treatment *(n=19)*
1	**Erythrocyte** *(M/mm^2)*	6.45±0.9	4.4±0.8	6.1±0.8***
2	**Haemoglobin** *(g/dL)*	13.8±1.0	9.1±0.3	12.5±0.9**
3	**Haematocrit** *(%)*	39.7±2.4	30.4±6.4	36.4±2.0**
4	**Total leukocytes** *(m/mm^3)*	9.2±0.8	8.6±0.4	9.1±0.5*
5	**Bilirubin** *(mg/dL)*	0.3±0.2	3.94±0.2	0.6±0.1***
6	**Glucose** *(mg/dL)*	119.6±6.2	87.4±5.0	115.5±5.1**
7	**ALT** *(U/l)*	17.4±1.5	51.0±8.0	17.2±1.6**

** p>0.05 – non-significant differences, ** p<0,05 – significant differences, *** p<0,01 – distinctly significant differences*

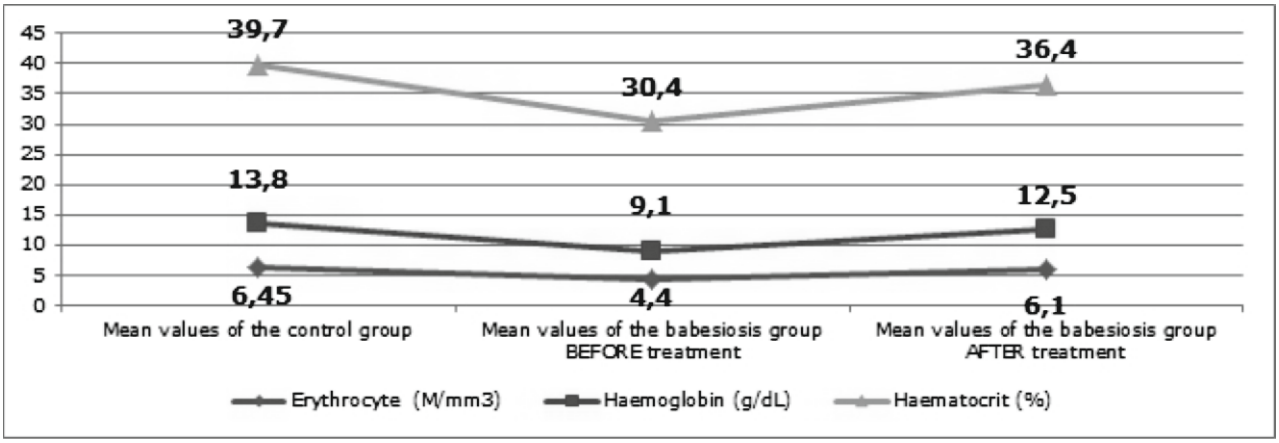

Fig. 1. Variations of the red line parameters mean values, before and after treatment in the studied group of dogs with babesiosis

be observed, and a statistically significant increase ($p < 0.05$) of the mean values of haemoglobin (12.5 ± 0.9 g/dl) and haematocrit (36.4 ± 2.0%), which again range between the characteristic limits of the species, a sign of remission of the anaemia and recovery of the haemoglobin load, aspects also described by other researchers. Worth mentioning is the fact that, after the symptomatic treatment was performed in order to correct the humoral imbalances induced by the hepatic and/or renal insufficiency, the parameters that attest the morphofunctional integrity of the liver and the nephron returned to values within the characteristic limits of the species (mean glucose value = 115.5 ± 5.1 mg/dl; mean value of ALT activity = 17.2 ± 1.6 U/I) (Table 2). The most important parameter that stood at the basis of the diagnosis of severe haemolytic anemia and the decrease of the hepatic function – bilirubin concentration - sign of erythrocyte degradation - 12 days after the initiation of specific treatment, shows a statistically significant increase of the mean value (p <0.01), falling within the characteristic limits of the species.

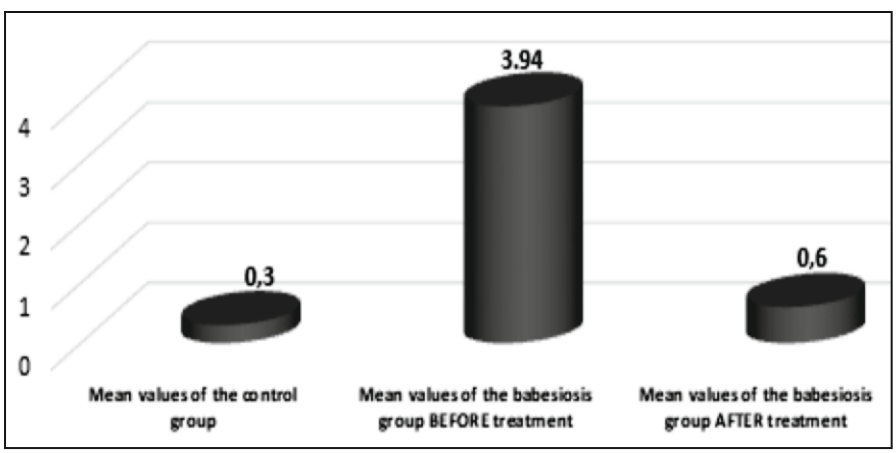

Fig. 2. Variations of the bilirubin's mean values (mg/dl) before and after treatment in the studied group of dogs with babesiosis

CONCLUSIONS

The efficacy of the medicinal products was demonstrated in all therapeutic schemes: (I) single dose (6.6 mg/kg) of Imizol, administered subcutaneously; (II) half dose Imizol (3.3 mg/kg) + clindamycin (30 mg/kg at 12 hours, for 5 days, then 30 mg/kg at 24 hours, for the further 16 days); and (III) the treatment only with clindamycin in the doses mentioned above. They led to the rapid and significant destruction of parasites in the body, but with a different recovery time, depending on the degree of infestation and also on the clinical signs manifested by each patient.

At 12 days after the initiation of the specific treatment, most of the patients displayed a distinctly significant increase (p <0.01) of the mean values of the red blood cells (6.1 ± 0.8 m/mm^3 blood) and a statistically significant increase (p<0.05) of the mean values of haemoglobin (12.5 ± 0.9 g/dl) and haematocrit (36.4 ±2.0%).

All the parameters that attest the morphofunctional integrity of the liver and nephron, evaluated at 12 days after the beginning of the treatment, have also returned to normal, falling within the characteristic limits of the species.

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