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Varsha Chauhan
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Brejesh Singh
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Kajal Jadav
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Amita Tiwari
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

RV Singh
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Rupesh Verma
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Corresponding Author:
Varsha Chauhan
Department of Veterinary Medicine, College of Veterinary Science and A.H., Jabalpur, Madhya, Pradesh, India

Comparative therapeutic efficacy of imidocarb and diminazene aceturate against *Babesia gibsoni* in dogs

Varsha Chauhan, Brejesh Singh, Kajal Jadav, Amita Tiwari, RV Singh and Rupesh Verma

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Abstract
The present study estimated the therapeutic management of *Babesia gibsoni* in the dog population located in and around Jabalpur (M.P.). A total of 2103 dogs that were brought to Veterinary Clinical Complex, College of Veterinary Science & A.H., Jabalpur and different government and private clinics of Jabalpur (M.P.) were screened for a period of six months (June 2021 to November 2021). 503 dogs found suspected based on clinical history *viz*. anorexia, fever, vomiting, diarrhoea, bleeding from the nostrils, pale of the mucous membrane, maelena, anaemia, jaundice, weight loss etc. and detection of the organisms in the blood of infected dogs and out of which 76 samples were haemoprotozoan positive amongst which 26 were *B. gibsoni* positive. For the therapeutic study, a total of 12 dogs confirmed for *B. gibsoni* were divided randomly into two treatment groups *i.e.*, T2 and T3, each comprising of 6 dogs. Dogs of group T2 and T3 were treated with Doxycycline @ 5mg/kg bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg bodyweight, PO, q12 h for 30 days +Imidocarb @ 6.6 mg/kg bodyweight, S/C, two doses14 days apart and Doxycycline @ 5mg/kg bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg bodyweight, PO, q12 h for 30 days + Diminazene aceturate @ 5 mg/kg bodyweight, I/M, two doses 48 h apart respectively. The best therapeutic response was observed in the T2 group. A blood smear examination reveals a lower the degree of Parasitemia on the 15th-day post-treatment and on the 30th-day post-treatment blood smear was negative in all affected dogs.

Keywords: Imidocarb, diminazene aceturate, *Babesia gibsoni*, dogs

Introduction
In India haemoprotozoa and rickettsia diseases are common in dogs due to favorable climatic conditions for parasites and vectors. Canine haemoprotozoal infection includes *Babesia gibsoni, B. canis, Hepatozoon canis* and *Trypanosoma evansi*. Canine rickettsial organism contains *Ehrlichia canis, E. iwangi, Haemobartonella canis* and *Anaplasma platys*.
Amongst various prevalent canine vector-borne diseases, canine babesiosis is a very common and clinically significant disease caused by intraerythrocytic apicomplexan protozoa belonging to the genus *Babesia*, distributed worldwide, including India. *Babesia* species are often referred to as piroplasm comprising two main species, *B*abesia *canis* and *Babesia gibsoni*, based on their size. *Babesia canis* is a large piroplasm (4-5 µm), which usually occurs as a single pear-shaped piroplasm or in pairs of merozoites divided by binary fission within the erythrocyte.
Many drugs have been tried successfully to effectively treat *canine babesiosis* e.g., Diminazene aceturate, Imidocarb dipropionate, Phentamidine, Phenamidine Isethionate, Trypanblue, Primaquone and Quinuronium sulfate etc. (Birkenheuer *et al.*, 2003) [2]. Imidocarb dipropionate is conventional therapy for babesiosis when used at 5-6 mg/kg by subcutaneous or intramuscular injection. Another combination commonly being used to treat canine babesiosis is Doxycycline-Enrofloxacin-Metronidazole with or without Diminazene aceturate (Vial and Gorenflot, 2006) [12]. Doxycycline in combination with diminazene aceturate has also been prescribed to treat *Babesia gibsoni*; however, a recent study found that persistent Parasitemia can still be detected in blood smears after this treatment (Birkenheuer *et al.*, 1999) [1].
According to the literature, no current therapeutic strategy has completely eliminated *Babesia gibsoni* infections. So, the study aimed to establish a clinically effective therapeutic strategy in canines.

Materials and Methods

For this study, a total of 2103 dogs that were brought to Veterinary Clinical Complex, College of Veterinary Science & A.H., Jabalpur and different government and private clinics of Jabalpur (M.P.) were screened for a period of six months *i.e.,* from June 2021 to November 2021. The dogs were screened for the presence of clinical symptoms *viz*. anorexia, fever, vomiting, diarrhoea, bleeding from the nostrils, pale of the mucous membrane, maelena, anaemia, jaundice, weight loss etc. The diagnosis was done based on blood smear examination, estimation of haemato-biochemical parameters along with molecular detection.

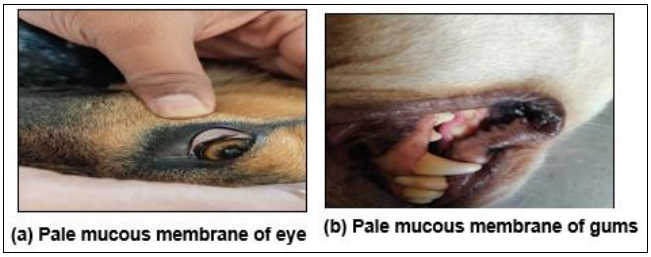

Plate 1: Mucous membrane examination of dogs affected with *Babesia gibsoni*

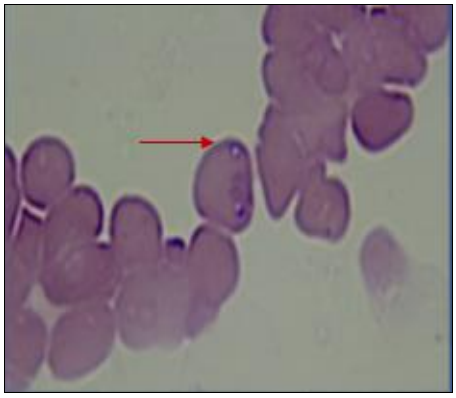

Plate 2: Blood smear showing *Babesia gibsoni*

Sample collection

Approximately 3 ml of blood samples were collected aseptically from a cephalic vein or from the tip of the ear from each canine. Out of which 1 ml was collected in a vial containing EDTA for routine hematology and DNA isolation. and 2 ml was collected in clot activator vials. Serum was harvested after centrifugation, frozen and stored at -4 °C until further biochemical analysis.

Microscopic examination

The blood smears were examined under 100x oil emersion fields (OIFs), results were interpreted as babesiosis when piroplasm of *Babesia gibsoni* or developing stages were found in at least one cell of erythrocytes. The blood smears were examined for intra-erythrocytic and extra-erythrocytic haemoprotozoa.

Experimental Design

Total of 12 dogs, after molecular confirmation for *Babesia gibsoni,* were selected for the study. These dogs were divided into two groups, each comprising 6 dogs. The T1 group includes 6 apparently healthy control. The efficacy of the drugs was evaluated based on improvement in clinical signs, alterations in hematological and biochemical parameters. Blood smear examination pre-treatment and post-treatment on 0,15th and 30th days.

Table 1: Therapeutic regimen

Groups	Drugs and Dosage	Number of animals
T1	Apparently healthy control	6
T2	Doxycycline @ 5mg/kg bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg bodyweight, PO, q12 h for 30 days +Imidocarb @ 6.6 mg/kg bodyweight, S/C, two doses14 days apart	6
T3	Doxycycline @ 5mg/kg bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg bodyweight, PO, q12 h for 30 days + Diminazene aceturate @ 5 mg/kg bodyweight, I/M, two doses 48 h apart	6

Supportive therapy included as an oral and parenteral antipyretic injection, B complex with liver extract, haematinics and fluid therapy.

Evaluation of Treatment

The parasitological examination was done on days 0, 15th and 30th by microscopy to evaluate the treatment outcome. The parasite was identified based on characteristic morphological appearance. The haemato-biochemical and urine examinations were carried out on days 0, 15th and 30th after initiation of treatment to evaluate the treatment response. Regression of symptoms was considered to evaluate the therapeutic outcome.

Results and Discussion

The study was conducted on a total of 2103 dogs of the irrespective breed, age and sex in the Department of Veterinary Medicine, Veterinary Clinical Complex (Co.V.Sc. and A.H., Jabalpur). The data obtained were statistically analyzed and presented. The following results were obtained from the study.

Clinical abnormalities of haemoprotozoal disease-affected dogs

During the study of haemoprotozoan diseases in dogs, various clinical abnormalities were observed among the affected dogs. All the affected dogs have shown the signs of anorexia 80.26 percent (61/76) followed by vomition 40.79 percent (31/76), weight loss 77.63 percent (59/76), pale mucous membrane 78.95 percent (60/76), enlarged lymph nodes 63.15 percent (48/76), tick infestation 69.44 percent (53/76), diarrrhoea in 43.42 percent (33/76) and epistaxis 39.47 percent (30/76) etc. Similar findings were also reported by Sudhakar Reddy *et al.* (2014) [9], Juripriya *et al.* (2019) [7] and Gonmei *et al.* (2020) [5] *i.e.,* fever, anorexia, pale mucous membrane, tick infection, vomition, hematuria and lethargy etc. Inappetence of anorexia observed in many dogs in a study, is a common non-specific sign of haemoprotozoan infection. This may be due to conspicuous weakness possible because of delayed presentation in the clinic and the owner's inadequate attention to the pets.

Comparative therapeutic efficacy

To evaluate the therapeutic efficacy of various combinations, a total of twelve dogs affected with *Babesia gibsoni* were randomly divided into two groups and treated with different combinations of drugs by using inj. Imidocarb and Diminazene. The efficacy of the drugs was evaluated based on improvement in clinical signs, alterations in hematological and biochemical parameters. Blood smear examination pre-

treatment and post-treatment at 0,15th and 30th days.

Group T2: The results obtained under the therapeutic study revealed that, out of two groups under study, T2 (Doxycycline @ 5mg/kg Bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg Bodyweight, PO, q12 h for 30 days +Imidocarb @ 6.6 mg/kg Bodyweight, S/C, two doses14 days apart) showed significant regression of clinical symptoms like fever within 24 hours, haematological and biochemical values gain normal within 30 days. Each blood smear was found negative indicating 100% recoverable by the 30th day of treatment. Similar findings were reported by Collett (2000) [4] and Schoeman (2009) [13], who recorded imidocarb, alone and in combination with other drugs, successfully treating canine Parasitemia. Imidocarb blockage of the entry of inositol into RBCs containing babesia resulting starvation of parasite and combination with DNA susceptible babesia caused nucleic acid damage.

Group T3: In treatment group T3 (Doxycycline @ 5mg/kg Bodyweight, PO, q12 h for 30 days +Metronidazole @ 15 mg/kg Bodyweight, PO, q12 h for 30 days + Diminazene aceturate @ 5 mg/kg Bodyweight, I/M, two doses 48 h apart) showed significant regression of clinical symptoms like fever within 24 hours, hematological and biochemical values gain normal within 30 days. Five blood smear was found negative indicated 83.33 percent recovery by the 30th day of treatment. Varshney *et al.* (2003) [11], Torbika *et al.* (2013) [10] and Joice *et al.* (201] also reported that treatment with diminazene aceturate at the dose rate of 3.5 mg/kg bodyweight single dose i/m in case of canine babesiosis infection resulted into significant regression of clinical symptoms like fever within 24 hours, haemoglobinuria, haematological values (HB, RBCs and PCV) were gain normal within 7 days. Diminazene interact with the minor groove of DNA double helix and interfere with the transcription and replication of DNA, leading to the death of parasites.

Table 2: Evaluation of comparative therapeutic efficacy of drugs in different groups by blood smear examination

S. No.	Groups (n=6 in each group)	Blood smear examination (absence of *Babesia gibsoni*)			
		Day 15	Recovery (%)	Day 30	Recovery (%)
1	T2 (Doxycycline +Metronidazole +Imidocarb)	6	100	6	100
2	T3 (Doxycycline +Metronidazole + Diminazene aceturate)	4	66.66	5	83.33

The efficacy of two drugs was evaluated based on blood smear examination *viz.* absence of piroplasm of *Babesia gibsoni* on the 15th day in all the six dogs of group T2 post-treatment. Each blood smear was found negative for babesia piroplasm indicating 100 percent recoverable by the 30th day of treatment. In dogs of group T3, it was noticed that 4 dogs on the 15th day of post-treatment, the absence of piroplasm of *babesia* in blood smear examination of 5 dogs. There was 83.66% recovery observed in dogs of the T3 group by the 30th day of treatment. Therefore, based on clinical recovery and restoration of haemato-biochemical parameters, the best therapeutic response was observed in the T2 group.

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