



Revista Electrónica:
Depósito Legal: ppi 201502ZU4665 // ISSN electrónico: 2477-944X

Revista Impresa:
Depósito Legal: pp 199102ZU46 / ISSN 0798-2259

UNIVERSIDAD DEL ZULIA
REVISTA CIENTÍFICA

FACULTAD DE CIENCIAS VETERINARIAS
DIVISIÓN DE INVESTIGACIÓN



MARACAIBO, ESTADO ZULIA, VENEZUELA



EVALUATION OF TRYPANOCIDAL AND ANTHELMINTIC EFFICACY OF AN ISOMETAMIDIUM – IVERMECTIN ASSOCIATION IN BOVINE

EVALUACIÓN DE LA EFICACIA TRIPANOCIDA Y ANTIHELMÍNTICA DE UNA ASOCIACIÓN DE ISOMETAMIDIUM E IVERMECTINA EN BOVINOS

Gustavo López-Valencia; Jesús Antonio Betancourt-Echeverry²; Elias Ascanio-Evanoff³; William Berrío-Cataño⁴; Andrés Felipe Velásquez-Arboleda⁵; Jorge Gómez-Oquendo⁶ and ⁷Gustavo Alonso López-Sierra⁷ Estadístico

¹Investigador independiente ²Escuela de Microbiología y Bioanálisis, Facultad de Salud Universidad Industrial de Santander ³Facultad de Ciencias Veterinarias, Universidad Central de Venezuela; Asesor Investigación y Desarrollo Reveex Group ⁴Dirección de Granjas, ⁵Politécnico Colombiano Jaime Isaza Cadavid, ⁶Politécnico and ⁷Colombiano Jaime Isaza Cadavid Director en GSBPO Chile.

E-mail: gulova851@gmail.com

ABSTRACT

The objective of the present work was to evaluate the efficacy of the compound Hemoveex® (isometamidium chloride 2,4% and ivermectin 2,0%) of Reveex, a Venezuelan laboratory, on the control of mixed infections of *Trypanosoma vivax* and gastrointestinal nematodes in bovine. Sixteen one year old heifers, assigned to two experimental groups (intramuscular (IM) and subcutaneous (SC)), were treated each with Hemoveex® at the dose of 1 milliliter (mL) /50 kg of body weight (BW); previously, all 16 heifers had been inoculated with 5 mL each of bovine blood showing 4 flagellates/100X microscopic field of *Trypanosoma vivax* initially obtained from a cow in Puerto Berrío, Antioquia, Colombia and further multiplied in a calf at the Jaime Isaza Polytechnic of Marinilla, Antioquia. The assignment to either group, was made on the basis of the “strongylid” nematode type egg per gram (epg) of faeces, using the McMaster technique. From day (d) 1 after treatment to d 63, when observations finished, no trypanosomes were seen in any of the sixteen heifers. As for the control of gastrointestinal nematodes, the association showed efficacies of 36, 12, 24 and 84%, on d 7, 28 and 42, and 63 post-treatment (PT), respectively, when applied by the IM route and of 47.8, 39.1 and 78.3%, on d 21, 28 and 63 PT, respectively, when administered (SC). Isometamidium + ivermectin was highly efficacious against *Trypanosoma vivax*, given either IM or SC presented a satisfactory anthelmintic efficacy only by d 63 PT.

Key words: Cattle; control; nematodes; test; trypanosomes

RESUMEN

El objetivo del presente trabajo fue evaluar la eficacia de la mezcla (cloruro de isometamidio al 2,4% e ivermectina al 2,0%) del laboratorio Reveex de Venezuela, en el control de infecciones por *Trypanosoma vivax* y nemátodos gastrointestinales en bovinos. Dieciséis bovinos de aproximadamente 1 año de edad divididos en dos grupos, por vía de inoculación intramuscular y subcutánea, fueron tratados con la mezcla isometamidio + ivermectina a la dosis de 1 mililitro (mL)/50 kg peso corporal; antes del tratamiento los 16 animales fueron inoculados vía venosa con 5mL cada uno, de sangre con una parasitemia de 4 parásitos por campo en frotis de sangre coloreado con Giemsa, de una cepa de *Trypanosoma vivax* adquirida en un bovino de Puerto Berrío, Antioquia, Colombia y multiplicada en un ternero en el Politécnico Colombiano Jaime Isaza Cadavid de Marinilla, Antioquia. La división de los grupos se hizo teniendo en cuenta los huevos de parásitos gastrointestinales tipo “strongylida” por gramo de heces, mediante la técnica de McMaster. Desde un día (d) después del tratamiento, hasta el d 63, cuando finalizaron las observaciones, en ninguno de los 16 animales se observaron tripanosomas. Con respecto al control de parásitos gastrointestinales, el producto mostró eficacias de 36; 12; 24 y 84% en los 7; 28; 42 y 63 post-tratamiento (PT), respectivamente, cuando se aplicó por vía intramuscular (IM) y de 47,8; 39,1 y 78,3% en los d 21; 28 y 63 PT, respectivamente, cuando se aplicó por vía subcutánea (SC). La mezcla isometamidio+ ivermectina resultó altamente eficaz contra *Trypanosoma vivax*; administrada tanto por vía IM; como SC y presentó una eficacia antihelmíntica satisfactoria sólo hacia el d 63 PT.

Palabras clave: Control; ganado; nematodos; prueba; tripanosomas

INTRODUCTION

Both, internal (gastrointestinal, pulmonary, hepatic, hematic, etc.) and external (ticks, flies, lice, mites, etc.) cause high economic losses to cattle industry worldwide.

Bovine (*Bos taurus*) trypanosomosis in Africa (caused mainly by *Trypanosoma vivax* (*T. vivax*) and *Trypanosoma congolense*), only in the Tse-Tse fly belt, causes losses estimated in United States of America (USA) \$ 4,75 billions/year (yr) [18]. In Colombia [5], where the disease is endemic in regions like Inter Andean Valleys, Middle Magdalena, Caribbean Coast and Eastern Plains [6], several studies confirm the economic importance of the disease. Betancourt and Wells [8] recall an episode of trypanosomosis in a dairy in the Cauca Valley where losses went up to USA\$ 5,654. Studies conducted in the State of Cordoba in 1996 found that, in three months, calves infected with *T. vivax*, gained an average of 6.0 kg less than non infected calves [1, 34].

Gastrointestinal worms severely affect the productivity of cattle ranches, since it produces anorexia, loss of blood and plasmatic proteins, lung damage, metabolic disturbance, diarrhea, and retarded growth [14, 40].

In South America, the control of *bovine* trypanosomosis has been based for many years on diminazene aceturate and, more recently on isometamidium chloride [11, 12]. Both compounds are of common use also in Africa [24, 25, 29] and are marketed as single molecules. Control of gastrointestinal parasitism (GIP) is mainly done with benzimidazol derivatives (albendazol, fenbendazol and others), imidazotiazols (levamisol, tetramizol), macrocyclic lactones (Ivermectinas, milbemicines), organophosphates (haloxon, triclorfon). All of them are also sold as single molecules. [13, 27, 33].

The colombian veterinary market does not have a compound containing both, isometamidium and ivermectin. Such a product would be useful, considering that a high worm burden produces immunodepression and could complicate a trypanosomosis clinical episode. Reveex Laboratory has developed a mixed product containing both drugs. It is expected that the product, while controlling gastrointestinal parasitism, favors the preventive and curative effect on trypanosomes. The present work was conducted to evaluate the efficacy of isometamidium and ivermectin combination, on the control of mixed infections by gastrointestinal parasites (GIP) and *T. vivax* in cattle.

Trypanosomosis

Bovine trypanosomosis produced by *T. vivax* is known in Colombia since 1931 [37, 49] and it is considered endemic in regions like: the Atlantic Coast, Cauca and Magdalena River Valleys and the Eastern Planes [6, 22, 34, 46] in warm zones and under 1500 meters above sea level (m.a.s.l.). Recently the presence of the parasite was reported in cattle in Antioquia, at 2.486 m.a.s.l. [50].

The disease has a strong economic impact due to abortions, anaemia, reduction of milk yield and control costs. [3, 4, 8, 9, 16, 34, 47].

Gastrointestinal parasites

Most known nematode genera have been reported in association with GIP in cattle in Colombia. In the Eastern Planes, *Cooperia*, *Haemonchus*, *Ostertagia*, *Oesophagostomum*, *Trichostrongylus*, *Trichuris*, *Bunostomum*, *Capillaria*, *Agriostomum*, *Toxocara* and *Mecistocirrus* have been found by different workers [32, 35, 39, 44]. In the Atlantic Coast, the genera *Strongyloides*, *Toxocara*, *Cooperia*, *Haemonchus*, *Mecistocirrus*, *Oesophagostomum*, *Bunostomum*, and *Ostertagia* have been registered in Cordoba State and the genera *Strongyloides*, *Haemonchus*, and *Trichostrongylus* in Cesar State [36, 41].

In the Middle Magdalena the genera *Strongyloides*, *Cooperia*, *Ostertagia*, *Haemonchus*, *Oesophagostomum*, *Trichostrongylus* and *Bunostomum* have also been found [13]. Another study conducted in Santander State, found that the most common nematodes infecting bovine in the García Rovira Province were *Toxocara*, *Cooperia*, *Haemonchus*, *Ostertagia*, *Nematodirus* and *Trichostrongylus* [38].

Generally speaking, GIP is more prevalent and severe in young calves. Villar and Arguelles [43], found the highest counts of eggs in faeces in calves 105 to 130 days (d). Some genera, like *Toxocara* and *Strongyloides*, are more common in younger calves [41, 44].

As for anthelmintics used in controlling GIP worms in bovine, studies in a milk producing area of Boyacá, found that Albendazol was the most commonly used (30%) [47], followed by ivermectin (14%) and levamisol (7%) [33]. Another work reported the oral use of 1% diatomaea sands as anthelmintic for cattle and reported 84 and 100% reduction in egg per gram (epg) of faeces count on d 90 and 135, respectively [28]. Marquez *et al.* [30], reported anthelmintic resistance in 25% of the farms examined at the Altiplano Cundiboyacense region. Resistance to albendazol and ivermectin was reported on 17 and 8% of these farms, respectively.

MATERIALS AND METHODS

The study was conducted at the Román Gómez Farm of the Jaime Isaza Cadavid Polytechnic in Marinilla, Antioquia located at 6°11'47" North; 75° 20' 0" West.

The drug tested: The Hemoveex® (Reveex Laboratories, Venezuela), compound tested on its trypanocidal and anthelmintic efficacy, is an association of isometamidium chlorhidrate 2,4% and ivermectin 2,0%. Ivermectin is an endectocide known for over 30 years. It works by stimulating the presynaptic GABA relaxation with the resultant blockage of the nervous impulse in the post-

synaptic transmission, leading to paralysis and death of the parasite. According to Gregorio's description, ivermectin binds to Cl⁻ ions regulated by glutamate (GluCl) located in muscular and nervous cells of invertebrates. This interaction leads to an increase in the permeability to Cl⁻ causing membrane hyperpolarization with paralysis and death of the parasite [21]. As for isometamidium, in the market for more than 50 yr, its mode of action is not fully understood. It is believed that selectively inhibits the kinetoplastic II topoisomerase of the trypanosome [10, 26]. Isometamidium also blocks nucleic acid synthesis [45]. Ivermectin and isometamidium have very different loci of action and work on very different processes; this discards any possible interaction between them.

Trypanosoma vivax strain: A *T. vivax* working strain was originally obtained from a natural infection in a cow at Puerto Berrío, Antioquia and kept in liquid nitrogen at the CES, Colombian Institute of Tropical Medicine.

Gastrointestinal nematodes: The study was performed using the natural nematode infections present in the calves when obtained for the study. Worm burdens were estimated on the basis of epg of faeces count using the McMaster Technique as described by Dunn [17]. Segmented eggs were named "strongylid" type, a term that includes eggs of the genera *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Cooperia*, *Mecistocirrus*, *Nematodirus*, *Bunostomum* and *Oesophagostomum* given the difficulty in telling them apart.

Experimental animals: Sixteen one year old heifers, *Bos taurus* crosses, with an average weight of 140 kilograms (kg) were obtained, kept stabled in the farm's facilities and fed fresh chopped grass, hay and commercial ration (2 kg/animal/d), salt and water *ad libitum*.

Inoculations with *T. vivax*: A heifer (Num. 0054) was treated on three consecutive d, with dexamethasone by the intramuscular (IM) route, at a dose rate of 0.1 milligrams (mg)/kg of body weight, and then inoculated intravenously (IV) with 5 milliliters (mL) of blood containing the working strain of *T. vivax* with a parasitaemia of 4.5 flagellates/100 X microscopic fields using an Olympus CX31 Japan equipment, as seen in a thin smear stained with Giemsa. From here onward, the blood of the heifer was examined daily or every other day to look for trypanosomes (in 50 microscopic fields of a thin smear) and to determine the haematocrit value. Body temperature was also measured at the same time. Once a high parasitaemia was observed, the remaining 15 heifers were inoculated IV, with 5 milliliters (mL) each of blood from heifer 0054, and monitored as described to determine clinical (temperature), haematological (haematocrit) and parasitologic (parasitaemia) values. Once parasitaemia with *T. vivax* was evident, all heifers were treated, either IV or IM, with Hemoveex®, at a dose rate of 1mL/50 kg BW, and monitored as described, on d [3, 7, 14, 21, 28, 42 and 63] post-treatment (PT).

Gastrointestinal parasites (GIP): On the same day of treatment

with isometamidium + ivermectin, all heifers were examined for gastrointestinal nematodes, using the McMaster technique. The heifers were assigned to either SC or IM group, depending on the route by which the compound would be applied. On the same d, a pool of faeces from those heifers showing the highest epg counts was submitted to cultivation by the Corticelli and Lai technique as described by Niec [31], to obtain L3 nematode larvae for further genera identification. Monitoring of GIP was done on the same PT d, described for *T. vivax*, and expressed in terms of epg of the "strongylid" type.

Efficacy: The efficacy of treatments was estimated as percentage parasitaemia and epg on each PT d, as compared with pre-treatment values for the same variables.

Weight gain: Body weight for each heifer was measured both, at the beginning and at the end of the study.

Statistical analysis Temperature, parasitaemia and haematocrit values, as well as eggs per gram (epg) and body weight data, before and after treatment, were compared by using the ANOVA test (analysis of variance), and accepting a significance level of 0,05 (5% error). All statistical calculations were made with the aid of the STATA program [2].

RESULTS AND DISCUSSION

Trypanosomes in donor heifer 0054

On d 11 post-inoculation, heifer 0054 presented a haematocrit of 26%, a body temperature of 39,0°C and a parasitaemia of 4,5 trypanosomes/field in a blood-stained smear. On this d, blood was collected with Ethylene Diamine Tetraacetic Acid (EDTA) as anticoagulant to inoculate the 15 remaining experimental bovines. Each heifer received IV 5 mL of parasitemic blood and was assigned to either the IM or the SC group.

Trypanosomes in the experimental heifers

On d six after inoculation, all heifers showed parasitaemia with *T. vivax*. The IM group, presented an average parasitaemia of 2.6 trypanosomes/field and the SC group presented an average parasitaemia of 5 trypanosomes/field on stained blood smears. The incubation period observed for *T. vivax* in the present work, was similar to that reported by different researchers in Africa and America [3, 6, 15, 23], especially when the infection is the result of IV inoculation.

On d 7 PT, eight heifers were treated IM and the remaining eight heifers SC, with isometamidium + ivermectin association at a dose rate of 1mL/50 kg of body weight. From d 1 PT to d 63 PT, no trypanosomes were seen in any of the experimental heifers with the Woo's [48] and Giemsa stained blood parasitological techniques employed. Parasitaemia readings on d 0 (treatment day) and until d 63 PT are presented on TABLES I and II, for the

TABLE I
***Trypanosoma vivax* PARASITAEMIA IN HEIFERS TREATED WITH**
ISOMETAMIDIUM – IVERMECTIN BY THE INTRAMUSCULAR (IM) ROUTE

Identification	Trypanosomes (N x microscopic field)							
	Experimental Days							
Animal Number	0	3	7	14	21	28	42	63
168	3,6	0	0	0	0	0	0	0
185	3,0	0	0	0	0	0	0	0
194	4,0	0	0	0	0	0	0	0
190	1,0	0	0	0	0	0	0	0
177	0,8	0	0	0	0	0	0	0
182	1,4	0	0	0	0	0	0	0
054	4,5	0	0	0	0	0	0	0
180	2,5	0	0	0	0	0	0	0
Total	20,8	0	0	0	0	0	0	0
Average	2,6	0	0	0	0	0	0	0

TABLE II
***Trypanosoma vivax* PARASITAEMIA IN HEIFERS TREATED WITH**
ISOMETAMIDIUM-IVERMECTIN BY THE SUBCUTANEOUS ROUTE

Identification	Trypanosomes (N x microscopic field)							
	Experimental Days							
Animal Number	0	3	7	14	21	28	42	63
183	13,0	0	0	0	0	0	0	0
187	1,6	0	0	0	0	0	0	0
009	15,0	0	0	0	0	0	0	0
186	3,8	0	0	0	0	0	0	0
179	0,1	0	0	0	0	0	0	0
189	2,0	0	0	0	0	0	0	0
192	2,5	0	0	0	0	0	0	0
175	2,2	0	0	0	0	0	0	0
Total	40,2	0	0	0	0	0	0	0
Average	5,0	0	0	0	0	0	0	0

IM and SC groups, respectively.

Efficacy

The absence of trypanosomes in the blood of all heifers from d 1 to d 63 PT, both in the IM and SC groups, demonstrated that under the conditions of the present study the association was 100% efficacious in controlling *T. vivax* infections in bovine, at least until d 63 PT. The early, 24 (h) curative effect provided by isometamidium has also been reported [42] and its efficacy as preventive and curative of infections with the parasite, as well as its long lasting protection, up to six months has been previously documented corchetes, [8, 11, 12, 15, 19, 20, 24, 29, 42].

Temperature readings

In the IM group, on the d of administration, being *T. vivax* present, five, out of eight heifers presented a body temperature $\geq 39^{\circ}\text{C}$, with an average for the group of 39.2°C . From here on, averages of body temperature for the group were 38.8, 38.5, 38.3, 38.6, 38.8, 38.5 and 39.0°C for the d 3, 7, 12, 14, 19, 21, 28, 42 and 63 PT, respectively (FIG 1).

In the SC group, on the day of the administration, being *T. vivax* present in all heifers, seven of eight animals had a body temperature $\geq 39.1^{\circ}\text{C}$, with an average for the group of 39.4°C . From here on, except for two heifers on d 3 PT, and one with wild behaviour

which was always hyperthermic, body temperature was normal, with averages of 38.7, 38.2, 38.4, 38.6, 38.8, 38.4 and 38.7°C on d 3, 7, 14, 21, 28, 42 and 63 PT, respectively (FIG. 1).

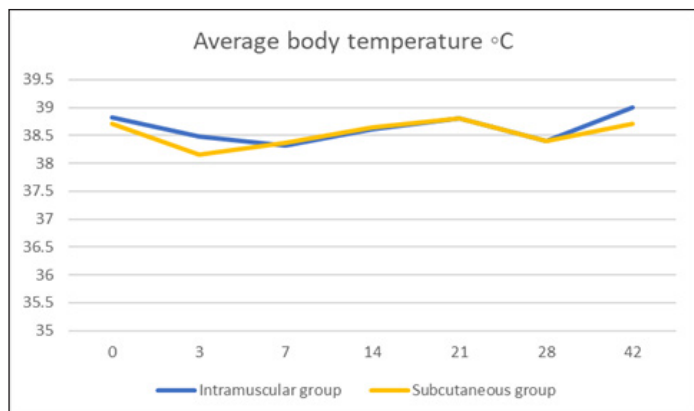


FIGURE 1. AVERAGE BODY TEMPERATURE ON HEIFERS TREATED WITH ISOMETAMIDIUM + IVERMECTIN BY INTRAMUSCULAR OR SUBCUTANEOUS ROUTE.

Haematocrit values

In the IM group, on the d of the administration, haematocrit values were normal, with an average for the group of 36.9%. From here on, the haematocrit increased until d 63 PT, with averages of 38.4, 45.4, 47.2, 50.6, 42.9, 45.2 and 49.1% for d 3, 7, 14, 21, 28, 42 and 63 PT, respectively (FIG. 2).

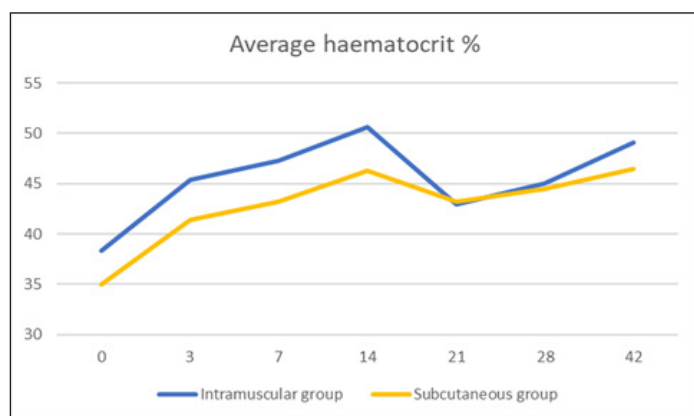


FIGURE 2. AVERAGE HAEMATOCRIT VALUES IN HEIFERS TREATED WITH ISOMETAMIDIUM + IVERMECTIN BY INTRAMUSCULAR OR SUBCUTANEOUS ROUTES.

In the SC group, on the d of treatment with isometamidium-ivermectin, the haematocrit values were normal, with an average for the group of 34.7%. From here on, the haematocrit increased reaching average values of 35.0, 41.4, 43.2, 46.2, 43.2, 44.5 and 46.5% for d 3, 7, 14, 21, 28, 42 and 63 PT, respectively (FIG. 2).

Gastrointestinal parasitism

Although early in the study *Moniezia* eggs and *Eimeria* oocysts were seen in some animals; they were not included in the results, since isometamidium + ivermectin has no effect on this type of parasites.

“Strongylid” type egg counts in both treated groups are presented in TABLES III and IV and FIG. 3. In the IM group, initial egg counts averaged 312.5. In terms of efficacy, the compound showed reduction of GIP on d 7, 28, 42 and 63 PT, the average efficacies being 36, 12, 24 and 84%, respectively. On d 14 PT, there was a marked increase in the epg values for the group, possibly due to eggs laid by adult worms that were on the larval stage in the intestinal mucose, on the day of the treatment (TABLE III).

Nematode eggs observed in the feces of heifers in the present work, were all of the “strongylid” type, which includes many of the genera reported by other workers [5,13,32,35,36,38,41,44]

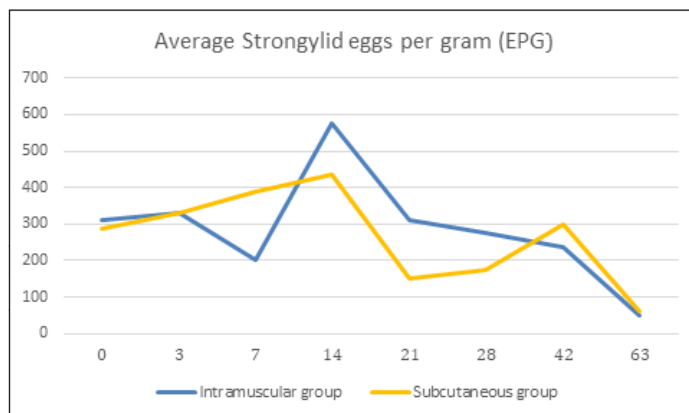


FIGURE 3. AVERAGE “STRONGYLID” TYPE EGGS PER GRAM OF FAECES IN HEIFERS TREATED WITH HEMOVEEX® BY INTRAMUSCULAR OR SUBCUTANEOUS ROUTE.

Cultivation of faeces

Cultivation of faeces yielded no L3 nematode infective larvae. For this reason, identification of nematode genera was not possible.

Statistical analysis

ANOVA test [2] did not show statistical (P<0.05) difference between IM and SC groups for the variables: parasitaemia with *T. vivax*, body temperature, haematocrit, nematode egg counts and weight gain.

TABLE III
NUMBER OF STRONGYLID TYPE EGGS PER GRAM OF FAECES IN HEIFERS
TREATED WITH ISOMETAMIDIUM-IVERMECTIN BY THE INTRAMUSCULAR ROUTE

Identification	Strongylid type (epg)							
	Experimental Days							
Animal number	0	3	7	14	21	28	42	63
168	700	400	200	200	300	200	300	50
185	400	400	300	1,600	800	500	100	50
194	100	250	200	400	300	200	200	50
190	350	50	300	1,400	200	500	300	50
177	250	0	100	0	0	100	100	0
182	350	400	200	500	500	200	600	0
054	100	250	100	100	200	200	300	150
180	250	900	200	400	200	300	0	50
Total	2500	2650	1600	4600	2500	2200	1900	400
Average	312,5	331,25	200	575	312,5	275	237,5	50
Efficacy %	-	0	36	0	0	12	24	84

TABLE IV
NUMBER OF STRONGYLID TYPE EGGS PER GRAM OF FAECES IN HEIFERS
TREATED WITH ISOMETAMIDIUM - IVERMECTIN BY THE SUBCUTANEOUS ROUTE

Identification	Strongylid type (epg)							
	Experimental Days							
Animal number	0	3	7	14	21	28	42	63
183	550	550	400	700	300	200	400	150
187	100	0	600	500	0	200	300	0
009	350	350	600	500	300	100	400	250
186	0	600	300	200	0	100	100	0
179	50	250	300	100	200	200	500	100
189	350	300	500	500	0	100	100	0
192	650	400	200	700	300	200	300	0
175	250	200	200	300	100	300	300	0
Total	2300	2650	3100	3500	1200	1400	2400	500
Average	287,5	331,25	387,5	437,5	150	175	300	62,5
Efficacy %	-	0	0	0	47,8	39,1	0	78,3

Undesirable reactions

No systemic or local undesirable reactions were detected in any of the heifers treated with the association, neither on the d. of treatment, nor on any of the post treatment d.

Weight gain

TABLES V and VI present the weight values for each heifer at the beginning and the end of the study in the IM and SC groups,

respectively. Confinement and suffering clinical tripanosomosis did not seem to have severely affected weight gain. In the IM group, average weight gain was 43.6 kg whilst in the SC group, it was 42.1 kg, during the 63 d of the study.

CONCLUSIONS

Isometamidium + ivermectin association was 100% efficacious in controlling *T. vivax* infections in cattle from the days following IM or SC administration to d 63 PT.

Body temperature and haematocrit values significantly improved in all trypanosome infected bovine after treatment.

TABLE VI
INITIAL AND FINAL BODY WEIGHT VALUES IN HEIFERS TREATED WITH
ISOMETAMIDIUM - IVERMECTIN BY THE SUBCUTANEOUS ROUTE

Animal Number	Initial Body Weight	Final Body Weight
183	181	239
187	138	190
009	120	150
186	148	168
179	150	179
189	136	174
192	144	216
175	148	186
Total	1,165	1,505
Average	145,6	187,7

In the first 21 d PT with the association given IM and 14 d PT given SC, anthelmintic efficacy of the compound was low, but then increased by d 63 PT and reached values of 84 and 78.3%, respectively.

The study did not reveal any difference in efficacy against trypanosomes and GIP nematodes between heifers treated by the IM or the SC route.

It seems that isometamidium + ivermectin, prevented weight loss in bovine suffering a clinical episode of tripanosomosis and a simultaneous infection with GIP nematodes. All treated heifers had gained weight significantly during the duration of the study.

The association did not cause any local or systemic undesirable reactions in bovine during the 63 d following its administration either by the IM or the SC route.

ACKNOWLEDGMENTS

The excellent collaboration of the staff and operative support personnel of the Jaime Isaza Cadavid Polytechnic in the Marinilla Farm and the financial and logistic support of Reveex, are highly appreciated.

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REVISTA CIENTÍFICA

Vol, XXX, N° 3

*Esta revista fue editada en formato digital y publicada en
Diciembre 2020, por La Facultad de Ciencias Veterinarias,
Universidad del Zulia. Maracaibo-Venezuela.*

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