Research Article

Therapeutic Evaluation of Fipronil and Doramectin against Brown Tick Infestation of Dogs

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Abstract | Hard ticks are ectoparasites which have a permanent relationship with their hosts. Ticks are spread of a variety of diseases that affect a wide range of animal hosts. In the current study, the acaricidal efficacy of topical Fipronil was evaluated compared to that of Doramectin injection on naturally infested dogs with hard ticks. Forty five stray dogs with age above 6 months were collected from Alexandria governorate with heavy or moderate ticks infestation. The captured dogs were divided into 3 groups, each group includes 15 dogs, and categorized as follows; group (1): (Positive control group), group (2): (Doramectin injected group), and group (3): (topical Fipronil group). It was observed that the overall complete curative rate was 60.00% in group 2 and 33.33% in group 3. Marginal Homogeneity test showed that there was a statistically insignificant difference between intervention groups pre and post-treatment as in group 2 (P=0.631) and group 3 (P=0.144). Furthermore, evaluating the efficacy of treatment using ROC curve showed that group 2 has a higher area under curve (AUC =0.742) than group 3 (AUC= 0.483). Both drugs were successful in controlling ticks in dogs, but Doramectin injection made a perceived influence on tick treatment in heavy infestation cases. In addition, Doramectin was found to be safer where it improved kidney and liver function tests in addition to the velocity of killing ticks with injection.

Keywords | Doramectin, Fipronil, Hard Ticks, Stray dogs, ROC curve

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INTRODUCTION

Rhipicephalus sanguineus is one of the brown hard ticks that infect stray dogs. It has a great medical and veterinary interest worldwide with sparked public and scientific concerns due to its direct health impact on its hosts through causing irritation, itching, dermatitis, and anemia as well as transmitting zoonotic diseases such as canine babesiosis, borreliosis, and anaplasmosis that can compromise both animal and human health. (Tan et al., 2021).

Furthermore, the limited published figures have revealed

the high prevalence rate of hard ticks in Egypt (89.4%) (Abdel Aziz et al., 2017). Various control strategies have been adopted to reduce the intensity of ticks by using acaricide which was increased dramatically during the previous decade such as combining many active ingredients to create a broad-spectrum anti-parasite or offering different modes of administration such as oral, injectable, and topical administration (Halos et al., 2014). Drug resistance is also becoming a major concern.

Topical Fipronil is one of the broad-spectrum chemical insecticides which belongs to the phenylpyrazole family that target the central nervous system of insects by inhibiting GABA-gated chloride and glutamate-gated chloride (GluCl) channels (Magalhães et al., 2018).

Moreover, the injectable solution of Doramectin is a macrocyclic lactone licensed and widely used for the control of ectoparasites in different animals like rabbits, alpacas, cattle, and swines by affecting the chloride ion channel activity in the nervous system of arthropods (Gordon et al., 2019). In addition, it is used to control canine generalized demodicosis in a dose of 0.3–0.6mg/kg SC and notoedreic mange in cats (Mark and Papich, 2016).

To the authors' knowledge, there are limited studies discussing the efficacy of products on stray dogs in Egypt. So, this study aimed at assessing the therapeutic efficacy and safety of topical Fipronil and Doramectin against ticks in naturally infested stray dogs.

MATERIALS AND METHODS

Animal inspection and sampling

Forty-five stray dogs above 6 months of age with a history of tick infestation were collected randomly from the center and west of Alexandria governorate, Egypt, and trapped in a registered animal house with registration number 584813328 under the control of the Ministry of Supply and Internal Trade, Alexandria. All respective animal protocols were reviewed by the state ethics commission and approved by a competent authority (The ethical committee FWA No: 00018699 and IRB No: 00012098, Faculty of Veterinary Medicine, Alexandria University, Egypt). The dogs included in this study were subjected to clinical examination including measuring body weight, temperature, and pulse. Blood was collected pre and post treatment from each dog aseptically from the cephalic vein and blood samples were used to perform complete blood count (CBC) analysis as well as liver and renal function tests. For group 1the blood samples were collected after one week of topical Fipronil administration. For group 2, blood samples were collected after one week from the second dose of Doramectin injection.

Identification of collected ticks

Ticks were identified using a stereomicroscope according to the available literature (Lord, 2011).

Treatment protocol

The captured canines were divided into three groups, each group includes 15 dogs: Group 1 (Positive control group) includes 12 highly and 3 moderately infested dogs and left un treated. Group 2 (Doramectin injection as standard treatment): include 11 highly and 4 moderately infested dogs and received Doramectin injection (0.6 mg/kg S/C) twice at two-week intervals. Group 3 (topical Fipronil as intervention treatment): include 10 highly and 5 moderately infested dogs were treated with topical Fipronil (a single dose of 0.1mL/kg) on dry intact skin between the shoulder blades and towards the skull base.

Cure assessment

The efficacy of treatment was determined based on measuring the intensity of infestation after treatment as follows; one to three ticks= low infestation, four to ten ticks= moderate infestation, and over ten specimens= high infestation (Costa-Junior et al., 2012).

Statistical analysis

Data were statistically analyzed using a Microsoft Excel spreadsheet and descriptive statistics. One-Way ANOVA was used for a quantitative dependent variable, z-Mann-Whitney U was used for non-normal distribution quantitative data between two groups, t-Paired Samples test were used for normal distribution quantitative data, and z-Wilcoxon were used for non-parametric quantitative data comparing two related samples. Monte Carlo test was used for calculating significance levels for the statistics available and Marginal Homogeneity test was used for non-parametric significance correlated samples. SPSS was used to analyze the data statistically. The significance level was considered at $P < 0.05$.

RESULTS AND DISCUSSION

The present study revealed that by a naked eye examination, 45 surveyed stray dogs exhibited ectoparasitism with various levels of intensity; 33 dogs (73.33%) were classified as highly infested cases and 12 dogs (26.66%) were classified as moderately infested cases. Clinically, it had been found that there were insignificant differences among infested dogs relative to age, weight, and pulse as depicted in Table 1. This finding may indicate the wide spread of brown ticks in the stray dogs included in this study and reflect their infection with blood protozoan parasite.

Regarding treatment assessment, a significant difference was observed in the reduction of brown tick infestation in

Table 1: medical parameter of infested stray dogs

Medical examination	Group 1 positive control	Group 2 Doramectin	Group 3 Fipronil	F	P
Age (months)	22±10.05	25.20±10.19	21.87±12.52	0 .186	0.831
Body weight (Kg)	18.17±3.288	17.07±3.97	18.23±4.017	0.452	0.640
Temperature(°C)	39.42±0.88	39.33±0.94	39.37±0.84	0.147	0.864
Pulse (Beats)	83±8.61	79.00±8.49	85.33±7.89	0.263	0.770

F= One-Way ANOVA

Table 2: Therapeutic efficacy of treatment of infested stray dogs

Treatment groups	Cured		non cured		Monte Carlo Sig. (2-sided)	
	no	%	no	%	Value	*P*
Group 2 Doramectin (n=15)	9	60.00	6	40.00	13.717	0.001*
Group 3 Fipronil (n=15)	5	33.33	10	66.67		

Table 3: Measurement the intensity of infestation of brown tick pre and post treatment

	Pretreatment		post treatment								*P* value
			Low		Moderate		high		completely cured		
Group 2 Doramectin	No	%	no	%	no	%	no	%	no	%	
Moderate	4	26.67	0	0.00	0	0.00	0	0.00	4	100.00	0.631
high	11	73.33	4	36.37	2	18.18	0	0.00	5	45.45	
Total	15	100	4	26.67	2	13.33	0	0.00	9	60.00	
Group 3 Fipronil											
Moderate	5	33.33	0	0.00	0	0.00	0	0.00	5	100.00	0.144
high	10	66.67	0	0.00	3	30.00	7	70.00	0	0.00	
Total	15	100	0	0.00	3	20.00	7	46.67	5	33.33	

Marginal homogeneity test

the Doramectin treated group where 60.00 % of infected cases were cured compared to 33.33% in the Fipronil treated group as illustrated in Table 2. This investigation indicated that Doramectin injection was more successful than topical Fipronil to eradicate the infestation of brown ticks. This can be attributed to the active ingredient in Doramectin which is fatal to ticks within 24 hours of treatment, with a peak level of 3 days after administration and remains at fatal levels for a minimum of 14 days after treatment. This causes ticks to skive during Doramectin application, persists throughout treatment, and drop out immediately after Doramectin injection. Doramectin injection was well-tolerated with minimum adverse effects such as ataxia (Davey et al., 2007, Moriello et al., 2017). Furthermore, earlier studies reported that the vitality of ticks which liberates following Doramectin injection is impaired up to 49 days after a single dose where ticks feed and deposit fewer eggs, with the viability of these eggs considerably reduced during this time (Davey et al., 2007). Additionally, these persistent lethal blood levels for injectable Doramectin are considered as excellent control over all tick stages and its persistent activity prevents ticks from binding for at least 28 days after treatment up to the laying stage.

Furthermore, the effect of treatment in the infestation intensity was displayed in Table 3 as follows; in group 2 (Doramectin injected group), 11 out of 15 dogs (73.33%) were highly infested and 4 (26.67%) were moderately infested before treatment. After treatment, 4 dogs (100%) of the moderately infested dogs and 5 of the highly infested dogs (45.45%) were totally cured. On the other hand, in the topical Fipronil treated group (group 3), 10 out of 15 cases (66.67%) were highly infested and 5 cases (33.33%) were moderately infested pre-treatment, while post-treatment, the 5 moderately infested dogs (100%) were totally cured, while none of the highly infested dogs was completely cured (0%). Although there was a reduction in ticks' infestation, it is worth noting that the Marginal Homogeneity test showed no statistically significant difference pre and post treatment among both topical Fipronil and Doramectin-treated groups (P = 0.631 and P=0.144, respectively). The lower efficacy of topical Fipronil compared to Doramectin injection could be attributed to the Fipronil being placed between the dog's scapula at the nape of the neck, leading to distributes and sequesters in the lipids of the skin and hair follicles after application. Also, it continues to be released on the skin and coat, resulting in long lasting tick activity where it reaches its highest concentra

Table 4: ROC curve to evaluate therapy effectiveness of one drug among infested dogs

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Group1 positive control	0.275	0.087	0.017	0.105	0.445
group 2 Doramectin	0.742	0.072	0.010	0.601	0.882
group 3 Fipronil	0.483	0.094	0.854	0.298	0.668

Table 5: the complete blood count (CBC) of infected dogs pre and post treatment with Doramectin and Fipronil

CBC findings		Infected dogs					
		Group 1positive control (n=15)		Group 2 Doramectin (n=15)		Group 3 Fipronil (n=15)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
RBCs (million/mm3)	Mean± SD	4.45±0.24	4.08±0.13	4.75±0.73	6.86±0.51	4.30±0.62	7.42±0.54
	t	-7.47		10.64		3.41Z	
	p	0.000*		0.000*		0.001*	
HB (g/dl)	Mean± SD	8.37±0.30	8.04±0.13	8.853±2.3646	12.893±1.4767	8.48±1.6201	12.327±1.3424
	t	-5.95		6.014		5.823	
	p	0.000*		0.000*		0.000*	
HCT (L/L)	Mean± SD	34.57±0.55	34.19±0.57	33.687±2.1954	43.747±6.7498	35.18±2.6304	47.26±4.2534
	t	-9.569		5.835		9.745	
	p	0.000*		0.000*		0.000*	
MCV (µm3)	Mean± SD	67.55±1.66	68.42±1.53	69.227±5.3048	74.773±8.7612	69.493±3.5292	84.293±11.68
	t	-6.984		1.69		5.349	
	p	0.000*		0.113		0.000*	
Platelets (mcL)	Mean± SD	298.26±36	281.86±38.20	364.33±172.912	390.40±131.416	226±202.933	293±173.309
	t	-6.745		0.455Z		0.998	
	p	0.000*		0.649		0.335	

Table 6: Liver and kidney function test findings of infested dogs pre and post treatment with Doramectin injection and topical Fipronil

Liver and kidney function test findings		Infested dogs					
		Group 1 positive control (n=15)		Group 2 Doramectin (n=15)		Group 3 Fipronil (n=15)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Uric acid (dL)	Mean± SD	2.23±0.24	2.59±0.22	2.752±1.2901	1.30±0.23	2.195±.9857	1.46±.1595
	t	11.271		-4.618		-3.135Z	
	p	0.000*		0.000*		0.002*	
Creatinine (mg/dL)	Mean± SD	1.33±0.06	1.33±0.06	1.415±0.1876	0.870±0.1119	1.259±0.2457	0.865±0.1113
	t	2.419		-10.455		-6.2	
	p	0.030*		0.000*		0.000*	
AST (SGOT) (U/L)	Mean± SD	120.93±5.32	131.13±6.41	122.8±12.885	54.47±13.958	117.87±9.635	58.13±14.422
	t	10.095		-16.478		-3.412Z	
	p	0.000*		0.000*		0.001*	

ALT (SGPT) (U/L)	Mean± SD	56.73±5.63	63.73±7.37	61.93±13.134	46.80±14.703	48.07±19.092	50.53±15.652
	t	11.202		-2.502Z		0.484	
	p	0.000*		0.012*		0.636	
ALP (U/L)	Mean± SD	78.73±7.57	85.73±6.70	97.88±41.8369	60.333±23.2768	73.587±35.0728	66.467±29.4615
	t	7.102		-3.682		-0.398Z	
	p	0.000*		0.002*		0.691	

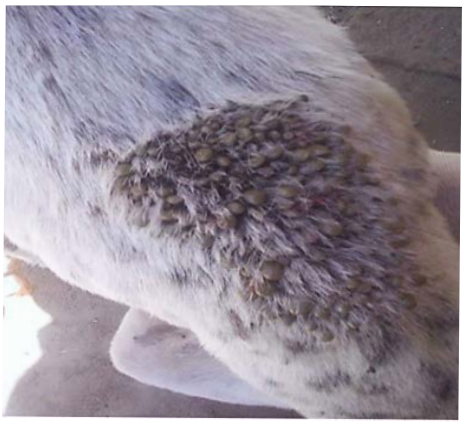

Figure 1: Heavy infestation of brown ticks in Doramectin group

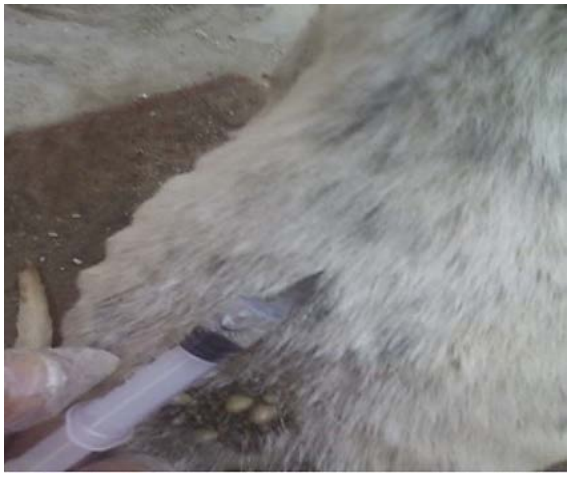

Figure 2: Administration of Doramectin subcutaneously

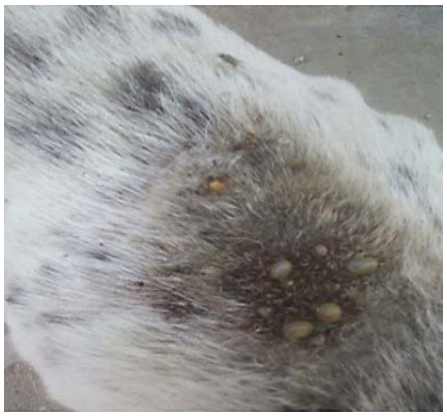

Figure 3: Heavy infestation change in to moderate infection after Doramectin injection

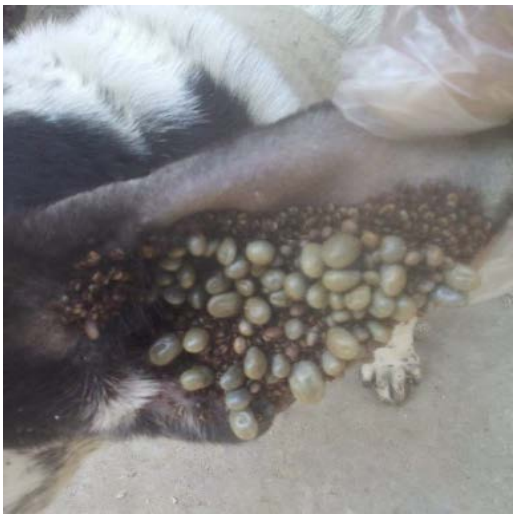

Figure 4: Heavy infestation of brown ticks in topical Fipronil group

Figure 5: topical Fipronil administration at back between the shoulder blades and near the skull base

tion on dog's hair 24 hours after single application, with a declining concentration trend and subsequently its residue lasts for about one month on the dog's hair. (Gupta, 2007). Furthermore, topical Fipronil is easily applied, but its effectiveness level may be impacted via water exposure during owner practices such as shampooing or bathing the dog, particularly those which live outdoor and may be exposed to a lot of water for health purposes. As a result, it's

vital to guarantee that a topical acaricide is effective for the duration of treatment interval which may require many immersions (Taenzler et al., 2016). Moreover, Fipronil was degraded by sunlight to create different metabolites, including Fipronil desulfinyl, which had an effect on tick ectoparasites. This metabolite is highly stable, more toxic, and bioaccumulates in adipose tissues (Ramesh and Gupta et al., 2018).

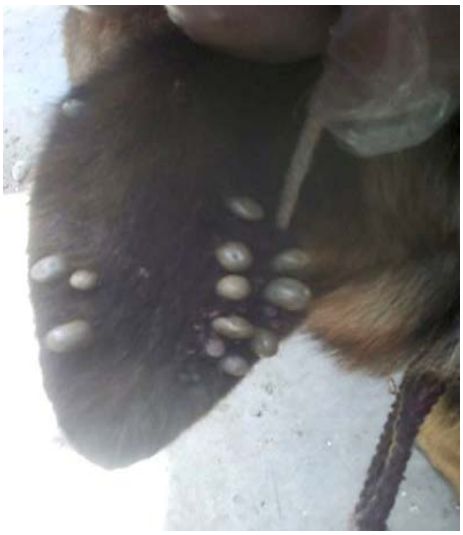

Figure 6: Heavy infestation change in to moderate infestation after topical Fipronil treatment

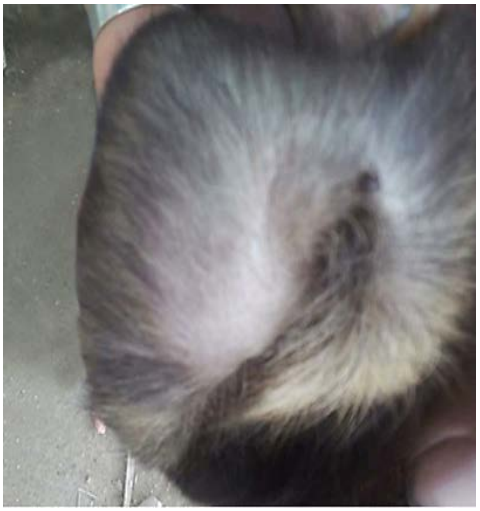

Figure 7: complete cure for moderate infestation after Fipronil treatment

Measuring the therapy effectiveness of Fipronil intervention in this study was also assessed using the ROC curve and the obtained result displayed in Table 4 showed that Doramectin injection was the winner where the area under the curve for Doramectin was higher than that of Fipronil (0.742).

Currently, the findings of blood parameters showed that in Doramectin and Fipronil treatment, a significant increase was observed in most of blood analyses post treatment, with exception to the analyses related to blood platelets, but the difference was statistically insignificant for both drugs as illustrated in Table 5.

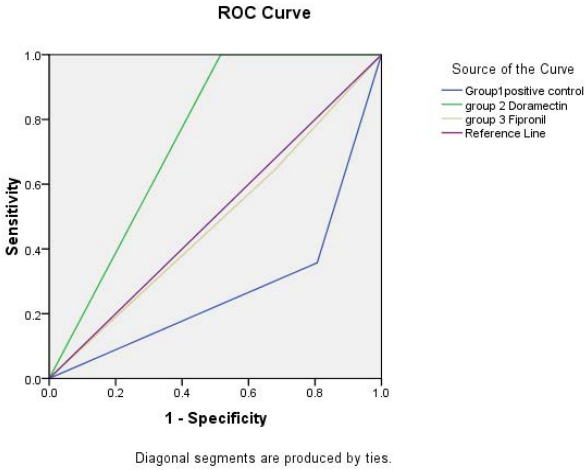

Figure 8: ROC curve to evaluate theraputic effectiveness of the intervention medications Doramectin and Fipronil in infested dogs through the area under the curve

Concerning the safety margin of Doramectin injection and topical Fipronil, kidney function tests revealed that in group 2, uric acid and creatinine levels significantly decreased post treatment (t = -4.618, P=0.000* and t = 10.455, P = 0.000*, respectively) compared to group 3 (t = -3.135Z, P = 0.002*, and t=-6.2, P=0.000*, respectively). Meanwhile, liver enzymes, particularly aspartate aminotransferase (AST) and alkaline phosphatase (ALP), were significantly decreased post-treatment in Doramectin and Fipronil treated groups. Although there was a significant reduction in the liver enzyme and kidney function test, Doramectin was found to be safer than Fipronil as displayed in Table 6. This result is in the same line with (George and Davey, 2004) who observed the safety of Doramectin on the renal and hepatic function tests and reduced the width of CBC analysis to normal values.

CONCLUSION

These preliminary findings provide useful baseline information for using Doramectin injection rather than topical Fipronil for brown tick control of infested dogs, particularly in heavy infestation cases, where it is safer in terms of kidney and liver function tests. Also, the current study indicated that topical Fipronil is more comfortable to apply and preferred to the moderately infested cases.

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NOVELTY STATEMENT

This is the first observation for therapeutic use of topical Fipronil in the treatment of brown hard ticks infestation in dogs in Egypt.

AUTHOR'S CONTRIBUTION

All authors equally contribute in designing the study, handling dogs, and writing the manuscript.

CONFLICT OF INTEREST

The authors declare there was no conflict of interest.

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