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Efficacy of combination of orally administered ivermectin (Neomac) and topically applied amitraz (RIDD® solution) against generalized demodicosis in dog

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Abstract
Canine demodicosis is a parasitic skin disease caused by an overpopulation of the host-specific follicular mites of the genus *Demodex*. Most cases of canine demodicosis are caused by *Demodex canis*, although two other species of demodex mites are reported. Localized demodicosis is a common mild and benign self-limiting disease. In contrast, generalized demodicosis is a serious and potentially life-threatening disease. Most cases of generalized demodicosis are juvenile in onset and develop in dogs less than 1 year of age. The present study was aimed to determine the efficiency of oral ivermectin and topical amitraz individually and a combination of both the drugs against generalized demodicosis in dogs. Study was conducted among 12 animals which were divided into three groups with four animals in each group. The different treatment regimens were adopted for 45 days. After 45 days of therapy, dogs treated with combination therapy showed quick recovery than the dogs treated with ivermectin or topical amitraz alone indicating the efficiency of combination therapy.

Keywords: Demodex, dog, ivermectin, amitraz, efficacy

1. Introduction
Canine demodicosis is an inflammatory parasitic skin disease caused by a proliferation of host specific follicular mite of the genus *Demodex* (Ferrer *et al*., 2014) [3]. This disease allows the mite to proliferate in the hair follicles and sebaceous glands leading to alopecia, erythema, scaling, hair casting, pustules and secondary infections (Koch, 2017) [7]. Canine demodicosis can be divided into two types : localized and generalized according to the extent of lesions. Canine generalized demodicosis (CGD) can be one of the severe canine skin disease requiring a prolonged treatment therapy (Kumari *et al.*, 2018) [9]. Canine demodicosis can be a challenge to treat due to several factors such as recurrence of disease after treatment (Morita *et al.*, 2018) [11], progression to generalized form (Ferrer *et al*., 2014) [3], immunosupression (Kumari *et al*., 2017) [9] and treatment duration (Paradis, 1999) [16]. It may be treated with either amitraz rinses (acaricide) or macrocyclic lactones such as ivermectins and milbemycin oximes (Tanrattana, 2017) [19]. Topical amitraz (at the rate of 0.025% to 0.06% once a week) is the only Food and Drug Administration (FDA) approved treatment and remains the only product licensed for this condition (Mueller *et al*., 2012) [12]. However, it is not always effective or well tolerated by affected animals which have intolerance to the licensed amitraz protocol (Paradis, 1999) [16]. Use of oral administration of milbemycin oximes (1-2 mg/ kg PO once a day) (Tanrattana, 2017) [19] and systemic endectocides like ivermectins at a dose rate of 0.3-0.6 mg/kg daily would provide an therapeutical alternative with similar cure rates (Paradis, 1999; Tanrattana, 2017) [16, 19]. Oral or injectable ivermectin, though not licensed for treatment of canine demodicosis, yet has been widely used and its efficacy was found to be excellent with cure duration of 3 months (Perego *et al.*, 2019) [18]. Milbemycin oxime, is a relatively safe treatment for generalized demodicosis with a cure rate of 85% (Holm, 2003) [5]; however it is expensive when used for this purpose. Recently, several combination therapies have been introduced in order to minimize the treatment duration and their efficacies has been tested in affected dogs (Perego *et al*., 2014; Beugnet *et al*., 2018; Becskei *et al*., 2018) [17, 2, 1]. Based on literature study, the present study was undertaken to evaluate the therapeutic efficacy of three different treatment protocols containing amitraz and invermectin in the management of canine generalized demodicosis.

2. Materials and Methods

2.1 Case presentation

Twelve dogs of different breeds within the age group from 5 months (mnts) to 5 years (yrs) were referrred to Veterinary Polyclinic, Changanacherry, Kottayam, Kerala with a history of severe pruritis and seborrhea of one month duration. Clinical examination of affected animals revealed foul smell from body, generalized exfoliative dermatitis associated with a multifocal, itchy, erosive and crusty dermatitis (Fig. 1). The total number of affected animals were divided into four groups containing four animals per group for analysis of physical and haemotological parameters. The parameters were described in Table 1.

Deep skin scraping were collected from the affected areas in 10% potassium hydroxide and submitted for microscopic examination. The skin scraping showed the presence of cigar shaped mite with body divisible into head, thorax bearing four pairs of short and stumpy legs and abdomen bearing transverse striations. The morphology confirmed it to be *Demodex spp* (Fig. 2). The case was diagnosed as generalized demodicosis.

Fig 1: Affected animals suffering from generalized demodicosis pre-treatment

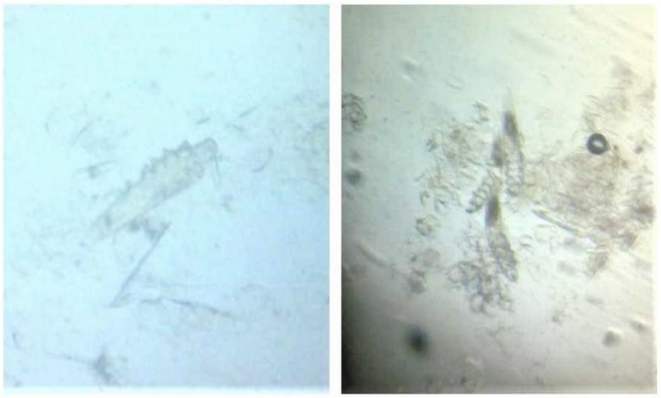

Fig 2: Photomicrograph of *Demodex spp* (100x) in Skin scrapings of affected animals

2.2 Treatment regimen

The affected animals of each group (Group 1, 2 and 3) containing four animals/ cases per group were given three different treatment regimens. Animals from group 1 were treated with ivermectin subcutaneous injection (Neomac injections) @ 0.2 mg/kg body weight every 7 days interval for 45 days. Animals from group 2 were treated with topical application of amitraz (RIDD®) @ 0.05% (4 ml of RIDD® diluted in 1 litre of water) by careful application into skin every five days interval for 45 days. Animals from group 3 were treated with oral ivermectin (Neomac tablets) @ 0.4 mg/kg bogy weight and topical application of amitraz (RIDD®) @ 0.05% every five days interval for 45 days. Each group of affected animals were observed daily for recovery of the clinical manifestation with respect to the different treatment regimens.

Table 1: Physical and haemotological parameters of affected dogs

Group 1.								
Case nos	**Species**	**Sex**	**Breed**	**Age**	**Coat color**	**Body weight (kgs)**	**Temperature (°F)**	**Pulse (per min)**
1	Canine	Male	Labrador	1yr	White	18	102.6	78
2	Canine	Male	GSD	3 yrs	Black and tan	24	102.2	86
3	Canine	Female	Pug	6 mnts	Cream	6	102	80
4	Canine	Female	Labrador	8 mnts	White	16	101.8	74
Group 2								
1	Canine	Male	Non descriptive	2 yrs	Brown	10	101.8	72
2	Canine	Male	Labrodor	3 yrs	White	25	101.6	80
3	Canine	Female	GSD	2 yrs 6mnts	Black and tan	20	102.0	78
4	Canine	Female	Non descriptive	3.5yrs	White	16	102.2	84
Group 3								
1	Canine	Male	Pug	1yr	Cream	18	102.8	72
2	Canine	Male	GSD	5 yrs	Black and tan	20	101.7	80
3	Canine	Female	Doberman	5 mnts	Black	9	102.3	78
4	Canine	Female	Labrador	8 mnts	White	16	102.8	84

3. Results

Animals from group 1 treated with subctaneous injection of ivermectin (Neomac injections) @ 0.2 mg/kg at 7 days interval, showed complete recovery on the 7th dose and took around 49 days after the start of the treatment. Group 2 animals treated with topical application of amitraz @ 0.05% (RIDD®) showed complete uneventful recovery at 10th dose i.e. at the end of 45 days. However, one animal from group 2

showed recurrence of clinical signs a week later after the treatment regimen has been stopped. Animals from group 3, treated with a combination of ivermectin oral therapy (Neomac tablets) @ 0.4 mg/kg bogy weight and topical application of amitraz (RIDD®) @ 0.05% every five days interval for 45 days showed complete recovery on the 7th dose (within 30 days) (Fig. 3). New hair growth on affected skin started after 15th day (4th dose) of start of treatment in group 3 animals. Though the subcutaneous injection of ivermectin and the combination therapy of oral ivermectin and topical amitraz cured the affected animals at their 7th doses, however the interval of dosage were different in both the treatment regimens.The combination therapy successfully applied to group 3 animals treated the disease within 30 days without any treatment related adverse effects as compared to subcutaneous injection of ivermectin that took around 45 days for complete recovery.

Fig 3: Hair re-growth in affected animals 30 days after treatment with combination of oral ivermectin (Neomac tablets) and topical amitraz (RIDD®solution).

4. Discussion

Canine demodicosis is a noncontagious parasitic skin disease caused by colonization of the host-specific follicular mites of the genus *Demodex*. Most cases of canine demodicosis are caused by *Demodex canis*, although two other species of demodicid mites has been reported (Kumari *et al*., 2018) [9]. Localized demodicosis is a common mild and benign self-limiting disease (White, 2011) [20], however the generalized form initiates with the progression of multifocal, erythematous, partially alopecic, crusted macules that eventuate in plaques and can be life threatening if left untreated. Several protocols have been used to treat generalized demodicosis viz. topical amitraz, systemic and oral ivermectins, imidacloprid/moxidectins and milbemycin oximes in various dosages (Paradis and Laperriere, 1992; Miller *et al*., 1993; Nayak *et al*., 2000; Holm, 2003; Mueller, 2004; Fourie *et al*., 2019) [15, 10, 14, 5, 13, 4]. Amitraz is currently the only treatment approved by FDA for canine generalized demodicosis (Horne, 2010) [6]. On the other hand, oral or subcutaneous ivermectins has been found to be safe, efficacious as well as cheaper to cure generalized demodicosis when compared to several other combination of drugs (Paradis, 1990). Therefore, in the present study, the efficacy of oral ivermectins and topical amitraz as a combination therapy along with the efficacy of ivermctin and amitraz singly has been evaluated in the treatment of generalized demodicosis in dogs. The results of the study revealed that the combination therapy of oral ivermectin and topical amitraz was found to be more effective than subcutaneous injection of ivermectin and topical amitraz alone. The combination therapy showed sucessful therapeutic mangement of generalized demodicosis with within 30 days of start of treatment without the use of any other supportative treatment. Our results were in support of previous study that uses combination regimen of ivermectin and amitraz for treating generalized demodicosis in dogs (Kumari *et al.*, 2018) [9]. However, they used subcutaneous injection of ivermectin and 12.5% amitraz and found the skin scrapping negative for mite on 42nd day after the start of the treatment.The results obtained in the current study were also in support with that of Paradis and Laperriere (1992) [15] and Mueller (2004) [13] who found ivermectin to be satisfactory to treat demodectic mange when given orally @ 0.3 to 0.6 mg/kg body weight.

5. Conclusion

A combination therapy of oral ivermectin (Neomac tablets) @ 0.4 mg/kg bogy weight and topical application of amitraz (RIDD®) @ 0.05% every five days interval for 45 days eliminated *Demodex spp*. mites on dogs with generalized demodicosis. Topical amitraz @ 0.05% every five days interval though successful in treating the affected animals at the end of 45 days, however recurrence of the clinicals symptoms occured after the treatment is discontinued, indicating that topical application singly might take a long duration of treatment to cure generalized demodicosis or might not be as effective as the combination therapy.

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