



First study of topical selamectin efficacy for treating cats naturally infected with *Brugia malayi* and *Brugia pahangi* under field conditions

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Abstract

Lymphatic filariae are important human and animal parasites. Infection by these parasites could lead to severe morbidity and has significant socioeconomic impacts. Topical selamectin is a semi-synthetic macrocyclic lactone that is widely used to prevent heartworm infection. Up until now, there were no studies that investigated the efficacy of selamectin in lymphatic filariae. Therefore, we aimed to study the chemotherapeutic and chemoprophylactic efficacies of selamectin use for cats in brugian filariasis-endemic areas in Southern Thailand. To assess chemotherapeutic efficacy of topical selamectin, eight *Brugia malayi* and six *Brugia pahangi* microfilaremic cats were treated with a single administration of topical selamectin. For chemoprophylactic efficacy assessment, a single application of topical selamectin was administered to 9 healthy, uninfected cats. The cats in both groups were subjected to a monthly blood testing for microfilariae and filarial DNA for 1 year. Topical selamectin treatment in *B. malayi* and *B. pahangi* microfilaremic cats showed 100% effectivity in eradicating microfilaremia but only 78.5% effectivity in eliminating filarial DNA. In the chemoprophylactic group, selamectin demonstrated 66.7% efficacy in preventing *B. malayi* infection. Our findings suggest that a single administration of 6 mg/kg topical selamectin given every two months could effectively prevent *B. malayi* infection. Application of topical selamectin twice a year could block circulating microfilariae. Since there are no treatment guidelines currently available for lymphatic filarial infection in cats, the data obtained from this study could be used to guide the management of brugian lymphatic filarial infection in reservoir cats.

Keywords Thailand · Selamectin · Chemotherapeutic · Chemoprophylaxis · *Brugia malayi* · *Brugia pahangi* · Macrocyclic lactone

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Introduction

Lymphatic filariasis (LF) is caused by filarial nematode parasites, i.e., *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. The parasites are transmitted to humans through the bite of infected mosquito vectors. It is the second leading cause of permanent and long-term disability worldwide (World Health Organization 1992). Lymphatic filariae have infected around 120 million people in 73 countries, and approximately 1.34 billion people live in areas where LF is endemic and are at risk of infection (World Health Organization 1992).

Lymphatic filarial infection in animals is mainly caused by *B. malayi* and *B. pahangi*. The parasites have developed in a variety of animal reservoirs, especially domestic cats, and are transmitted by mosquitoes (Chansiri et al. 2002; Laing et al. 1960; Mak et al. 1982; Mak 1984). While *B. malayi* is a causative agent of LF in humans; *B. pahangi* infection seems

to be restricted to domestic cats and wild animals. However, a few studies have reported the presence of *B. pahangi* microfilariae (Mf) in blood samples of people living in Malaysia, Indonesia, and Thailand (Palmieri et al. 1985; Muslim et al. 2013; Sagarasaerane et al. 2017). In addition, there has been a report revealing *B. pahangi* as a cause of LF in humans (Tan et al. 2010). Thus, appropriate prophylaxis should be given to *B. pahangi*-infected cats to prevent possible zoonotic transmission to humans (Al-Abd et al. 2015).

In brugian filariasis-endemic areas in Southern Thailand, wild and domestic cats have been reported to be naturally infected with *B. malayi* and *B. pahangi* (Wongkamchai et al. 2014; Sagarasaerane et al. 2017). Thus, domestic cats may serve as natural reservoirs of zoonotic filariasis in the areas. It is possible that cats naturally infected with *B. malayi* may play a key role in re-emergence of brugian filariasis and, to some extent, zoonotic infections caused by *B. pahangi* (Chansiri et al. 2002; Chittrakarn et al. 2009; Khowawisetsut et al. 2017). This emphasizes the urgent need to focus on elimination of lymphatic filariae as well as prevention of new or recurrent infection in cats and other natural reservoirs to reduce zoonotic transmission (Wongkamchai et al. 2014).

Ivermectin is widely used as a drug of choice for filariasis control and treatment in human and animals (Campbell 1982; Kwarteng et al. 2016). Nevertheless, treatment options of ivermectin are limited by the fact that it effectively kills microfilariae but demonstrates limited adulticidal activity (Kimura 2011; Khowawisetsut et al. 2017). Moreover, from our observation, oral administration of ivermectin may trigger nausea and vomiting in some recipient cats. This side effect may decrease drug compliance which leads to treatment failure.

Selamectin is a semi-synthetic macrocyclic lactone (ML) (Fisher et al. 2007) affecting glutamate-gated chloride ion channels (GluCl_s) that are present in neurons and pharyngeal muscles of nematodes, either activating the channels directly or potentiating their responses to glutamate (Cully et al. 1994, 1996). For *B. malayi*, more recent data have indicated that the GluCl_s exist in the excretory/secretory pore of microfilaria and the reproductive tissue of the adult worm (Moreno et al. 2010; Li et al. 2014). The drug causes rapid clearance of microfilariae as well as long-term sterilization of the female worm by inhibiting the secretion of immunomodulatory molecules (Moreno et al. 2010; Li et al. 2014) which leads to suppression of the Mf population for several months (Wolstenholme et al. 2016).

Selamectin is considered safe for use in both large and small animals and in pregnant and lactating cats and dogs because it does not cross the blood–brain barrier in mammals and achieves large volume distribution, tissue penetration, and accumulation in sebaceous glands, thereby acting as a drug reservoir (Gupta 2007). Although selamectin and ivermectin are both macrocyclic lactones, selamectin has been modified

to improve its safety profile (Krautmann et al. 2000). Topical selamectin is easier to administer than either oral or parenteral ivermectin, and its toxicity has been reported to be lower (Fisher et al. 2007).

Since ivermectin is the current drug of choice to treat cats with lymphatic filariasis, we postulated that topical selamectin would show similar efficacy in treating this disease. However, no guidelines exist for the treatment of lymphatic filarial infection with selamectin. Accordingly, we investigated the chemotherapeutic and chemoprophylactic efficacies of topical selamectin for cats naturally infected with *B. malayi* and *B. pahangi* in brugian filariasis-endemic areas of Southern Thailand.

Materials and methods

Animal ethical approval

The study protocol was approved by the Animal Ethics Committee of the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. SI-ACUP 024/2556). This study complied with all of the principles set forth in The Ethical Principles for the Use of Animals for Scientific Purposes which were issued by the National Research Council of Thailand (NRCT) in 1999.

Recruitment of the study animals

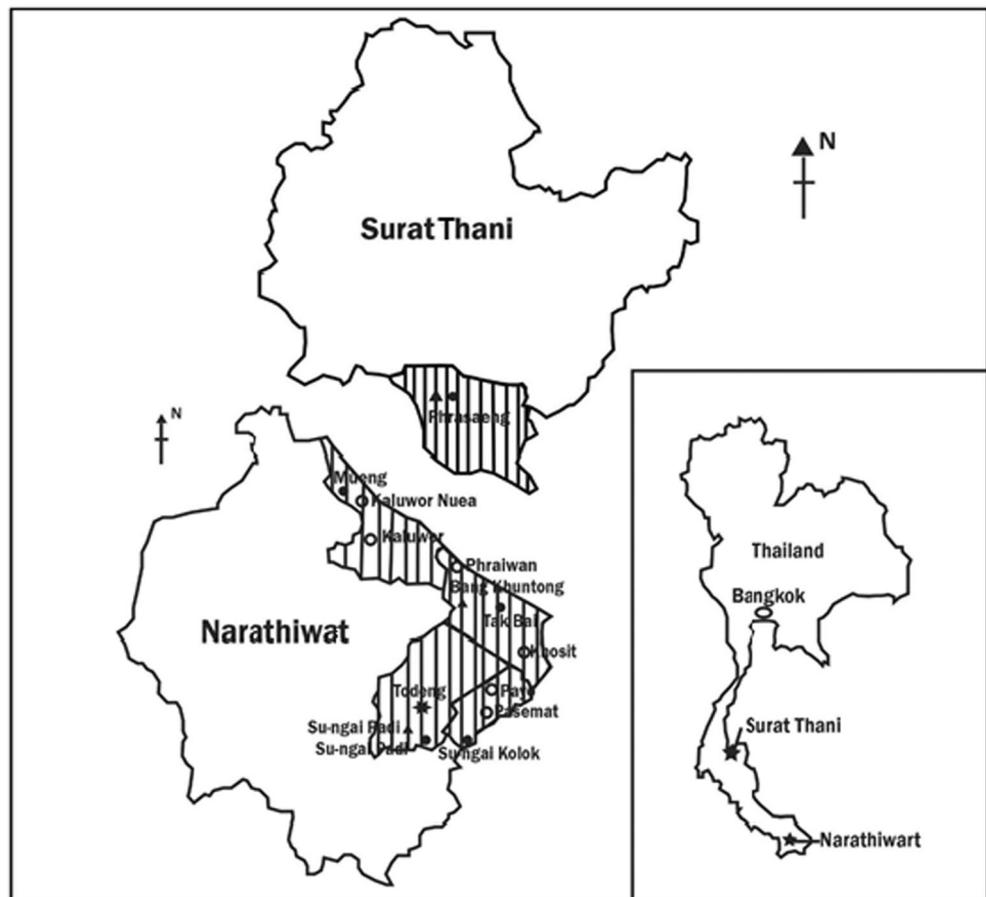
This study was performed in Tak Bai and Sugaipade Districts, Narathiwat Province, and Phrasaeng District, Surat Thani Province, in Southern Thailand (Fig. 1) during October 2016 to March 2018. A total of 23 cats were enrolled in the study.

For the study of chemotherapeutic efficacy of topical selamectin, eight *B. malayi* microfilaremic cats (CN1–CN8) were randomly recruited from pet owners in Tak Bai and Sugaipade Districts, Narathiwat Province. Six *B. pahangi* microfilaremic cats (CS1–CS6) were randomly recruited from Phrasaeng District, Surat Thani Province.

For the study of chemoprophylactic efficacy, nine healthy uninfected cats (UN1–UN9) were randomly selected from Tak Bai and Sugaipade districts, Narathiwat Province. We chose Tak Bai and Sugaipade districts as study areas because the cats that stayed in these areas were at risk to be infected with *B. malayi* (from our previous surveys in the years 2014 and 2017, the prevalence rates of *B. malayi* infection in cats in these areas are 2.9 and 3.3%, respectively) (Wongkamchai et al. 2014; Wongkamchai, unpublished data, 2017).

The average weights of the study cats were between 3 and 3.5 kg. No cats included in this study had received any preventive agents within 3 months of the start of the study. Pregnant and lactating cats, cats in poor general health, and cats with systemic diseases unrelated to brugian infection

Fig. 1 Map of Surat Thani and Narathiwat Province showing the study areas (● district, ⊙ sub-district, ▲ study area, ★ Todeng swamp forest)



were excluded. Clinical examinations were performed at the beginning and at subsequent time points during the study.

Detection of *B. malayi* and *B. pahangi* in cats

Detection of *B. malayi* or *B. pahangi* in study cats was performed using blood taken from an ear of each cat. Thick blood smear staining technique was used to detect parasite microfilariae, and high-resolution melting (HRM) real-time PCR was performed to confirm parasite species and detect parasite DNA (mitochondrial 12S rRNA genes of filarial worms) (Wongkamchai et al. 2013).

Microfilariae counts by thick blood smear Giemsa staining

Fifty microliters (μL) of blood samples were prepared for thick blood smear. Giemsa staining was performed according to the standard published WHO procedure (World Health Organization 1992). Microfilariae were detected using microscopic examination. The microfilariae (Mf) density was determined and expressed as the number of Mf in 1 mL of blood.

High-resolution melting real-time PCR analysis

Filarial DNA was extracted from 60 μL of the cat's ear blood samples using the high pure PCR template preparation kit (Roche, Germany). The concentration of the extracted DNA was measured by Nanodrop spectrophotometric procedure (Thermo Fisher Scientific). Extracted DNA was used as a template in high-resolution melting (HRM) real-time PCR (Wongkamchai et al. 2013). The forward and reverse primers recognized a 115-bp region of the mitochondrial partial 12S rRNA genes (forward, 5'-TTTAAACCGAAAAAATATTGACTGAC and reverse, 5'-AAAACTAAACAATCATACATGTGCC) of *B. malayi* and *B. pahangi*. These genes contain genus- and species-specific sequence variations useful for identifying the two filarial species (Fig. 2). Sequences were obtained from the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov; accession number for *B. malayi*, AJ544843.1, and *B. pahangi*, AM779849.1) (Wongkamchai et al. 2013). The HRM real-time PCRs were performed in a single run on a Light-Cycler LC480 instrument (Roche Diagnostics, Penzberg, Germany) as previously described (Wongkamchai et al. 2013). Briefly, 10 μL reaction mixture contained 3 μL of DNA, 0.25 pmol of each primer, and 3 mM MgCl_2 in 5 μL of the LightCycler 480 High-

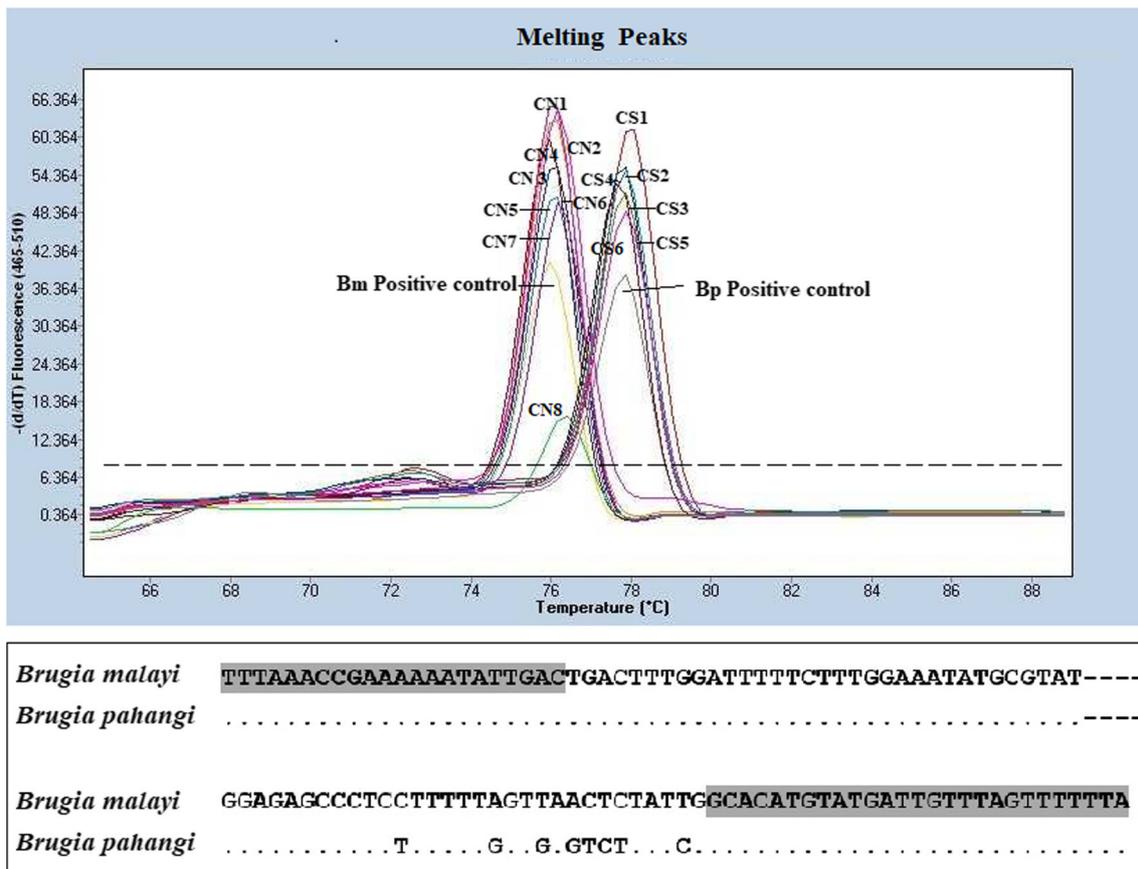


Fig. 2 HRM results of the study samples. The graph shows melting peaks of *B. malayi* DNA (CN1–CN8) and *B. pahangi* DNA (CS1–CS6). Bm and Bp peaks represent positive control cats and alignment of partial mitochondrial 12S rRNA gene sequences of *B. malayi* (GenBank

accession number AJ544843; positions 177–287) and *B. pahangi* (GenBank accession number AM779851; positions 154–264), respectively. Dots indicate identity; dashes indicate deletion from the above consensus sequence; and gray areas indicate primers

Resolution Melting Master mixture containing ResoLight dye (Roche Diagnostics) nuclease-free water that replaced the DNA template for negative controls. The reaction conditions included a denaturation step at 95 °C for 5 min followed by a 40-step amplification for 10 s at 95 °C, 10 s at 58 °C, and 10 s at 72 °C. Subsequently, the products were heated to 95.8 °C for 1 min and, then, cooled to 40 °C for 1 min. HRM was performed from 65 to 95 °C. The final cooling step was 40 °C for 10 s. The positive controls (one *B. malayi* microfilaremic and one *B. pahangi* microfilaremic cat blood samples) were used as positive controls for DNA extraction and HRM real-time PCR.

Chemotherapeutic efficacy of topical selamectin

Eight *B. malayi* microfilaremic cats (CN1–CN8) and six *B. pahangi* microfilaremic cats (CS1–CS6) received a topical application of selamectin (Revolution®; Zoetis, Inc., Parsippany, NJ, USA) to the skin at the base of the neck in front of the scapulae at a dosage of 6 mg/kg, on days 1, 15, 30, and 45 (Table 1). All cats were observed at 1, 2, 4, and 6 h after treatment for any clinical changes or adverse events, including mydriasis, salivation, depression, anorexia, vomiting, diarrhea,

unsteadiness, ocular discharge, squinting, abnormal breathing, muscle tremor, and pruritus.

Chemoprophylactic efficacy of topical selamectin

Nine uninfected cats (UN1–UN9) received a single dose of 6 mg/kg topical selamectin (Revolution®; Zoetis, Inc.) on day 1 at the beginning of the study (Table 1). The cats were observed at 1, 2, 4, and 6 h after receiving treatment for any clinical changes or adverse events, including mydriasis, salivation, depression, anorexia, vomiting, diarrhea, unsteadiness, ocular discharge, squinting, abnormal breathing, and muscle tremor.

Management and post-treatment follow-up

Topical selamectin administration and care of the animals were performed by the cat owners at their household. Coded sign was hanging around the animal's collar and was used for identification. All cat owners were informed about the study protocol and objectives and provided written informed consent. All owners were trained regarding when and how to

Table 1 The treatment protocol in *B. malayi* and *B. pahangi* naturally infected cats, and the prevention protocol in *B. malayi* naturally infected cats

Treatment purpose	Dose	Timing of drug administration
Chemotherapy	Selamectin 6 mg/kg single dose	Day 1
		Day 15
		Day 30
		Day 45
Chemoprophylaxis	Selamectin 6 mg/kg single dose	Day 1
Control	No treatment	–

B. malayi, *Brugia malayi*; *B. pahangi*, *Brugia pahangi*

apply the provided topical selamectin to their cats. Blood samples were taken from the ear of each cat before, during, and after treatment with topical selamectin. Blood samples were used for microfilariae detection by Giemsa-stained thick blood smear examination and for filarial DNA detection by HRM real-time PCR.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Differences in the variables at baseline and follow-up of the same individual were compared using the Wilcoxon signed-rank test. Two-tailed *P* values < 0.05 were considered significant.

Results

Chemotherapeutic efficacy of topical selamectin

Of all 16 cats recruited in this study, nine were infected with *B. malayi* and the rest were infected with *B. pahangi* as confirmed by Giemsa thick blood smear examination and HRM real-time PCR. The microfilarial densities of *B. malayi*- and *B. pahangi*-infected cats varied from 40 to 3640 and 20 to 4300 Mf/ml, respectively (Fig. 3a,b).

At 1 month after receiving the first dose of topical selamectin, two out of eight *B. malayi*-infected cats (25%; CS4 & CS6) showed a complete microfilarial clearance and were negative for filarial DNA by HRM real-time PCR at 1 month after the start of treatment (Fig. 3a, Fig. 4, and Supplementary Table 1). The majority of the cats (62.5%; CN1, CN4, CN6–CN8) in this group showed a complete clearance of microfilariae and were negative for filarial DNA after completing the 3-dose treatment course. Interestingly, one cat (12.5%; CN5) showed undetectable microfilaremia at 1 month but filarial DNA was still positive

at 12 months after the start of treatment. The rest of the cats in this group (25%; CN2 & CN3) had delayed microfilaria clearance and filarial DNA were still positive until the end of the study (Fig. 3a, Fig. 4 & Supplementary Table 1). Cat CN2 was amicrofilaremic at 8 months but filarial DNA was still detectable up to 12 months over the study period (Fig. 4 & Supplementary Table 1). Cat CN3 became negative for microfilariae within 8 months post-treatment; however, filarial DNA was still detectable up to 9 months after the initial dose of selamectin (Fig. 4 & Supplementary Table 1).

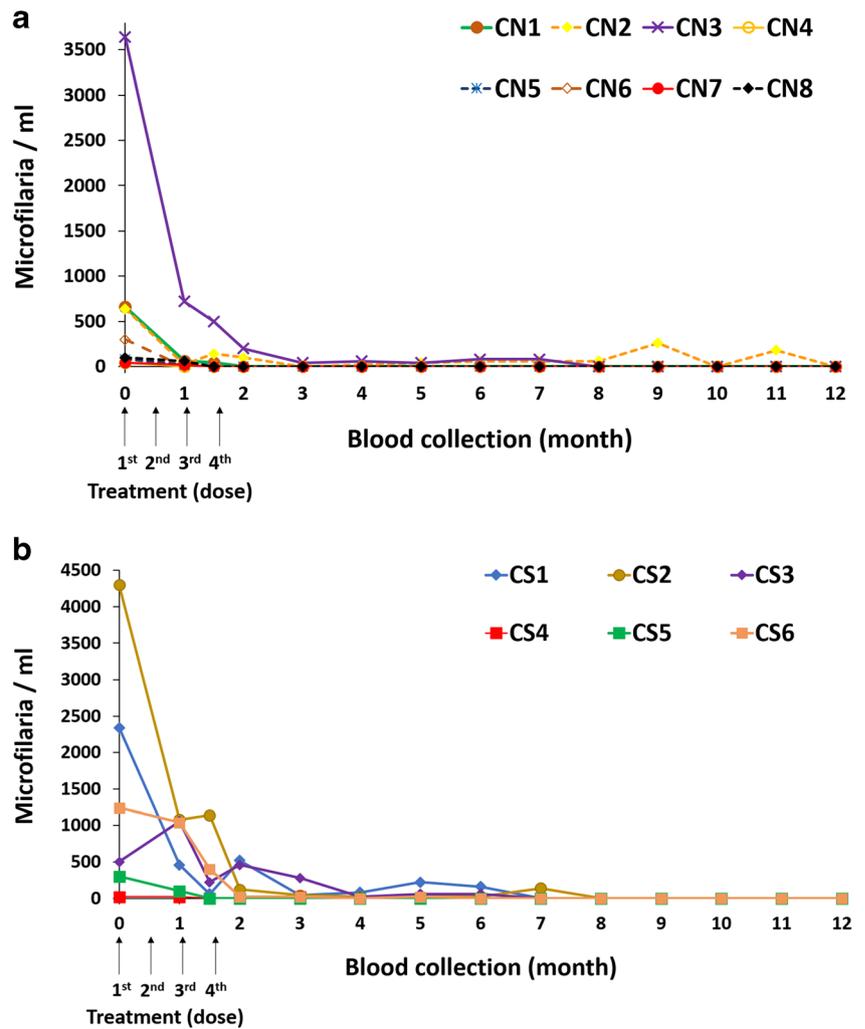
In *B. pahangi*-infected group, of the six cats that received topical selamectin for treatment, two (CS5 and CS4) were completely clear of microfilariae at 1.5 and 3 months, respectively, and they were negative for filarial DNA at 2 and 8 months after the start of treatment (Fig. 4; Supplementary Table 1). Cat (CS6) showed a complete clearance of microfilariae within 6 months after treatment but filarial DNA was still detectable until the end of the study period. Cats (CS1 & CS3) showed complete elimination of microfilariae within 7 months, and cat CS2 was completely clear of microfilaria within 8 months after the start of treatment. Filarial DNA remained detectable in cat CS1 at 10 months, cat CS2 at 8 months, and cat CS3 at 9 months after selamectin treatment. No circulating microfilariae were detected in any of the cats in this group within 8 months after they received topical selamectin treatment.

Overall, microfilarial levels at 1 month after topical selamectin treatment were significantly lower than the pre-treatment levels in all study cats (CN1–CN8, CS1–CS6) ($P = 0.009$) (Fig. 3a,b & Supplementary Table 1). The earliest clearance period of *B. malayi* (CN4) and *B. pahangi* (CS5) microfilaremia was within 1 and 1.5 months after the start of selamectin treatment (Fig. 3a,b & Supplementary Table 1). At the end of the study, filarial DNA remained detectable in 2 cats (CN2, CN5) in the *B. malayi* treatment group and 1 cat (CS6) in the *B. pahangi* treatment group (Fig. 4 & Supplementary Table 1).

Chemoprophylactic efficacy of topical selamectin

B. malayi DNA was detected in one of nine (UN1–UN9) healthy uninfected cats at 2 months after receiving topical selamectin (Fig. 5). One cat became positive for *B. malayi* microfilariae at 8 months after prophylactic treatment and remained positive until the end of the study (Fig. 5). Two cats were DNA positive at months 7 and 12, but *B. malayi* microfilariae were not detected in either of those 2 cats (Fig. 5). A single application of 6 mg/kg selamectin was effective at preventing the development of *B. malayi* in the remaining 6 cats until the end of the study. Therefore, topical selamectin showed 66.7% effectivity in preventing *B. malayi* infection in the 9 healthy, uninfected cats.

Fig. 3 a,b Microfilarial density (Mf/ml) of *B. malayi* (2a; CN1–CN8) and *B. pahangi* (2b; CS1–CS6) treated with selamectin during the study period



Discussion

The most effective strategy to eliminate lymphatic filariasis in endemic areas is to diminish the parasite in its natural reservoirs and attempt to reduce or interrupt transmission to

humans. Therefore, eradication of microfilariae in domestic cats in the endemic areas is essential for long-term control of lymphatic filariasis (Wongkamchai et al. 2014).

In the present study, topical selamectin was evaluated for its chemotherapeutic efficacy against naturally infected cats as

Fig. 4 Percentage of *B. malayi* (blue lines)- and *B. pahangi* (red lines)-infected cats treated with selamectin as detected by the presence of microfilaria in thick blood smear (dense lines) or HRM real-time PCR (dash lines)

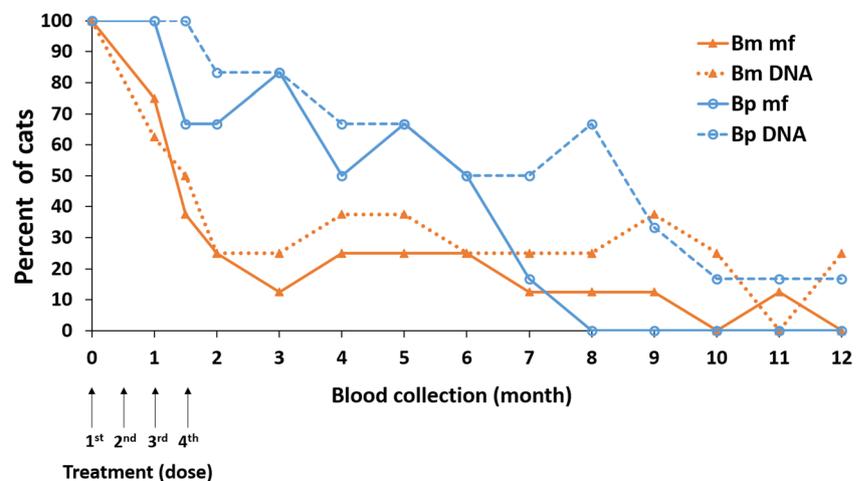
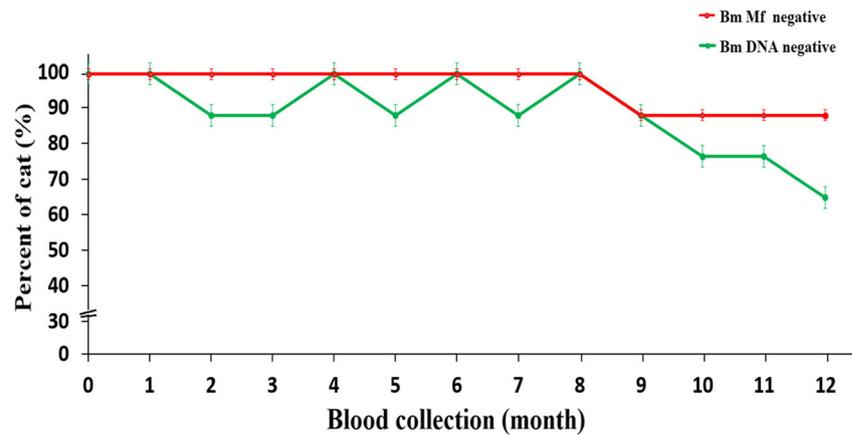


Fig. 5 Percentage of *B. malayi* uninfected cats after receiving topical selamectin prophylaxis as determined by the presence of microfilaria in thick blood smear (clear bars) or HRM real-time PCR (orange bars)



well as its chemoprophylactic efficacy in uninfected cats under field conditions. A dose of 6 mg/kg selamectin was chosen because it is the minimum recommended dosage for topical use in cats.

Topical selamectin showed 100% chemotherapeutic efficacy against circulating microfilariae of *B. malayi* and *B. pahangi*. Nevertheless, three microfilaremic cats that received topical selamectin were still positive for parasite DNA at the end of the study which implies the presence of the worms in the infected cats. Selamectin belongs to the macrocyclic lactone family (ML) that acts mainly against the larval stages of filarial parasites. The MLs have limited effects on adult worms, other than long-term sterility, that can lead to temporary suppression of the Mf population (Wolstenholme et al. 2016; Awadzi et al. 2014; Chandrashekar et al. 2014; Tompkins et al. 2010; Ottesen 2006). Absence of circulating microfilariae in this study might be due to the direct microfilaricidal effect of selamectin, and the effect of long-term sterility on adult female worms. Although infection may still occur, the reduction of circulating Mf can decrease transmission of the lymphatic filarial parasites from infected cats to insect vectors (Ottesen 2006). Thus, topical selamectin seems to be a promising option to reduce microfilariae in the blood of infected cat to levels that cannot sustain transmission of LF through mosquito vectors. Nevertheless, intermittent treatment is required.

A prophylactic treatment guideline for lymphatic filariasis in cats is currently unavailable. Thus, we decided to determine the efficacy of a single dose of 6 mg/kg topical selamectin treatment on lymphatic filariasis in cats. The results of the present study showed that a single application of topical selamectin demonstrated 66.7% efficacy for preventing *B. malayi* infection (negative for both microfilaremia and filarial DNA).

One cat was positive for the filarial DNA at 2 months after receiving topical selamectin and became microfilaremic 7 months thereafter. This suggests that the cat became infected after the application of selamectin since no microfilariae nor filarial DNA were detected in this cat prior to treatment.

Moreover, the prepatent period (the period between infection with the parasite and the demonstration of the blood microfilariae) has been estimated to 3.5 months for *B. malayi* (Partono 1987; Wongkamchai et al. 2016). Therefore, we suggest that topical selamectin should be reapplied every two months to prevent filarial infection or twice a year to block circulating microfilariae.

Selamectin demonstrates 100% effectivity in preventing *Dirofilaria immitis* (dog heartworm) infection in the endemic areas of the United States and Italy (Moraes-da-Silva Mde et al. 2016; Boy et al. 2000; Clemence et al. 2000). In another study, forty-six healthy uninfected dogs in a high-risk area received eight consecutive monthly applications of topical selamectin, which prevented heartworm in 73.3% of the dogs (Labarthe et al. 2015).

Notable differences between the present study and others include filariae species, studied animals, and treatment protocol. Most studies have focused on determining the therapeutic efficacy of selamectin on heartworm treatment in dogs, whereas this study aimed to evaluate chemotherapeutic and chemoprophylactic efficacies of this drug on zoonotic lymphatic filariasis in cats. In addition, only single application of topical selamectin was used in this study, while repeated doses of selamectin at 8, 12, and 30 months were administered in other studies.

A clinical practice guideline for heartworm prevention recommends a monthly application of topical selamectin on cats and dogs (Nelson et al. 2005). However, intermittent application of selamectin monthly may be challenging in low socioeconomic areas due to its cost. Our study suggests that administration of topical selamectin twice a year could effectively block circulating microfilariae and may reduce transmission of filarial parasite to subsequent insect vectors.

Conclusions

This study is the first to investigate the chemotherapeutic efficacy of topical selamectin in cats naturally infected with

lymphatic filariae caused by *B. malayi* or *B. pahangi* and the chemoprophylactic efficacy against *B. malayi* infection in healthy, uninfected cats in filarial-endemic areas. Topical selamectin showed 100% effectivity in eliminating circulating microfilariae of *B. malayi* and *B. pahangi* in all treated cats. These data suggest that topical selamectin could be used for preventing transmission of *Brugia* from infected cats to subsequent mosquito vectors. For chemoprophylaxis, our findings suggest a single administration of topical selamectin every two months to prevent filarial transmission or twice a year to reduce circulating microfilariae. Since there are no treatment guidelines currently available for lymphatic filarial infection in cats, the data obtained from this study could be used to guide the management of brugian lymphatic filarial infection in domestic cats.

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Availability of data and material All data generated or analyzed during this study are included in this published article and supplementary table.

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Compliance with ethical standards

Consent for publication Not applicable.

Competing interests The authors acknowledge the financial support from a Zoetis–Siriraj Joint Grant. Zoetis provided financial support for the field study, and Siriraj provided financial support for the laboratory analyses. Zoetis does not endorse the use of selamectin other than in strict accordance with the information provided on the product label.

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