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RESEARCH ARTICLE

Effectiveness of the Combination of Imidacloprid/ Moxidectin/ Praziquantel and Moxidectin/ Praziquantel Applied Topically in Dogs with Endoparasites and Ectoparasites

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Abstract:

Background:

Topically applied antiparasitic drugs used in dogs have evolved in terms of active ingredients, but progress has also been made through the development of drugs that control both ectoparasites and enteroparasites (nematodes and cestodes).

Objective:

The aim of this study is to evaluate the effectiveness of Moxidectin 3.5g/ Praziquantel 10.0g and Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g combinations applied topically in dogs with helminths (cestodes and nematodes) and ectoparasites, respectively.

Methods:

A total number of 276 dogs were analyzed. Dogs with nematodes or cestodes were treated with Moxidectin 3.5g/ Praziquantel 10.0g. All the positive cases for ectoparasites were treated with Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g.

Results:

The effectiveness of Moxidectin/ Praziquantel was $\geq 99.8\%$ from day 14 to day 35 on all the nematodes analyzed. The effectiveness of Moxidectin 3.5g/ Praziquantel 10.0g for *Dipylidium caninum* was significant on day 7 (75%) and reached 100% by day 14. A significant efficacy for *Taenia* spp. was achieved by day 7 and 100% from day 28 AT. Eighty-three dogs tested positive for 11 classes of ectoparasites. The Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g treatment proved to be effective in all the ectoparasites from day 7, until reaching 100% effectiveness by day 14 in the *Linognathus setosus*, *Ctenocephalides canis*, *Amblyomma americanum*, *Ixodes* spp., *Rhipicephalus sanguineus*, and *Dermacentor reticulatus* sp. We found a positive correlation ($r = 0.7430$, $p < 0.0001$) between the pruritus scale and lesion scale.

Conclusión:

The use of Moxidectin 3.5g/ Praziquantel 10.0g applied topically was effective against nematodes and cestodes. Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g was effective against ectoparasites and pruritus.

Keywords: Canine, Ectoparasites, Endoparasites, Pruritus, Spot on , Drugs.

Article History

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1. INTRODUCTION

Dogs can harbor a large number of gastrointestinal parasites [1], many of these are zoonotic, and this is why they

are considered a public health problem worldwide [1 - 4]. In addition, dogs can also have ectoparasites of clinical and zoonotic importance [5]. Therefore, antiparasitic treatments appear to be significantly effective. Topically applied antiparasitic drugs used in dogs have evolved in terms of active ingredients, but progress has also been made through the development of drugs that control both ectoparasites and

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enteroparasites (nematodes and cestodes) [6]. Some studies have evaluated the chemical compatibility and the dermal and systemic safety of external application drugs that contain Moxidectin/ Imidacloprid as active ingredients having beneficial results [7]. Nowadays, combinations of new topical formulations, that could be useful to control ectoparasites and endoparasites in dogs, are available; nevertheless, there are few studies on the effectiveness of these presentations. This research aims to evaluate the effectiveness of Moxidectin 3.5g/ Praziquantel 10.0g and Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g combinations applied topically in dogs with helminths (cestodes and nematodes) and ectoparasites, respectively.

2. MATERIALS AND METHODS

This study was conducted from May to October 2021 at the Parasitology Laboratory of the DERMAVET Veterinary Hospital, in Mexico City, Mexico.

2.1. Animal

Two hundred seventy-six dogs varying in breed, gender, and health conditions were evaluated. One hundred and ninety-one of these dogs had positive results in their feces samples for cestodes and nematodes, eighty-three dogs were with ectoparasites. All the patients' owners signed a consent agreement that explained the aim and goals of the study and we conducted an epidemiological survey.

2.2. Analysis of Samples

All the feces samples were analyzed individually with the techniques of direct smear with and without dyeing (Lugol's iodine) [8], Faust's centrifugal-flotation using a zinc sulphate solution 33% (SG 1.18) [9], and acetate tape to detect parasitic forms [10]. The feces samples were carefully examined under a light microscope with 10x, 40x, and 100x objective lenses, field by field crossing all microscope slides, and all the samples were analyzed twice. It was classified as a positive sample when at least a parasitic form was seen. Feces sampling and serial analysis were performed on all the animals on days 0 (previous to the treatment), 7, 14, 28, and 35 after the treatment (AT).

All the dogs received a dermatological examination, an analogous evaluation of pruritus, identification of lesions, and the presence of ectoparasites with the following techniques: acetate tape test [11], deep and superficial skin scrapes, and Trichogramma [12, 13], as well as direct observation of ectoparasites with a light source and a magnifying glass. The visual analogous scale of pruritus used was described by Hill *et al.* [14]. To evaluate pruritus, a visual analogue scale was used with a score from 0 to 10, 0 being "no itching, no scratching, no chewing, no rubbing nor licking" and 10 being "constant itching, scratching, chewing, rubbing or licking". The scale of lesions registered the clinical evaluation in 62 places in the body and then each sign was rated on a scale from 0 to 5 as follows: (0) negative, (1) mild, (2-3) moderate, and (4-5) severe. In this evaluation, the highest attainable score was $62 \times 4 \times 5 = 1240$. All the dogs were serially evaluated on days 0, 7, 14, 21, 30, and 35 AT.

2.3. Treatments

All the dogs that tested positive for nematodes or cestodes were treated with a single application of Moxidectin 3.5g / Praziquantel 10.0g (Canis Endo spot[®] LABYES) used in the form of *spot-on*, directly onto the skin, applied in an area from the upper neck to the lower neck, to avoid licking the product, additionally, dogs that presented some protozoa were treated with 15 mg of Metronidazole, PO; BID, for 7 days. All the dogs that tested positive for ectoparasites were treated with a single application of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g (Canis Full spot[®] LABYES) directly onto the skin on the area from the upper to the lower neck. This was done so that dogs could not lick the product.

2.4. Statistical Analyses

The data of each evaluation was concentrated in a data sheet and later analyzed through the Fisher's exact test to compare between AT weeks by each genus of nematodes and cestodes, the data of ectoparasites were compared by proportions and percentage of decrease and to compare the pruritus scale per week and the lesion score per week after the treatment using the Tukey's studentized range test. To set up the correlation between pruritus and lesions, we used Pearson's correlation coefficient by means of the Statistical Analysis Software, SAS 8.0.

3. RESULTS

3.1. Animals

The study included 275 dogs, out of which 191 dogs tested positive for at least one parasitic form in their feces samples, in this group, 107 were female and 84 were male, aged between 3 and 12 months old, 117 were pure breed, and 74 were mixed breeds. There was no association or difference between these variables in the presence of intestinal parasites. Eighty-three dogs presented some external parasitic form, in this group 41 were female and 43 were male between 3 and 12 months old, 48 were pure breed, and 36 were mixed breed, and there was no association in the presence of ectoparasites.

3.2. Effectiveness of the Combination of Moxidectin 3.5g/ Praziquantel 10.0g Against Nematodes

Dogs tested positive for five genera of nematodes: *Toxocara canis*, *Ancylostoma caninum*, *Uncinaria* sp, *Trichuris vulpis*, and *Strongyloides stercoralis*. The effectiveness and persistence of the treatment with Moxidectin 3.5g/ Praziquantel 10.0g on the intestinal nematodes in dogs are presented in Table 1. There was a significant difference in the effectiveness from day 7 AT against the five nematodes analyzed (average effectiveness of $\geq 77.25\%$) having greater efficacy in the treatment against *Uncinaria* sp. (89.48%) and *Trichuris vulpis* (87.5%). The effectiveness of Moxidectin/ Praziquantel was $\geq 99.8\%$ from day 14 to day 35 AT on all the nematodes analyzed.

3.3. Effectiveness of the Combination of Moxidectin 3.5g/ Praziquantel 10.0g Against Cestodes

Out of the 191 dogs included in the study, some animals

tested positive for two genera of cestodes: *Dipylidium caninum* and *Taenia* spp. The effectiveness and persistence of the treatment with Moxidectin 3.5g/ Praziquantel 10.0g on the intestinal cestodes in dogs are presented in Table 2. The

effectiveness of Moxidectin 3.5g/ Praziquantel 10.0g for *Dipylidium caninum* was significant by day 7 AT and reached 100% by day 14 AT. A significant efficacy for *Taenia* spp. was achieved by day 7 AT and 100% from day 28 AT.

Table 1. Effectiveness and persistence of the combination of Moxidectin 3.5g/ Praziquantel 10.0g to treat dogs with nematodes.

	Start	Days after Treatment			
	0	7	14	28	35
<i>Toxocara</i> spp.	-	-	-	-	-
Positive	134a	33b	4c	2c	1c
Effectiveness (%)	0	75.38	97.02	98.51	99.26
	-	-	-	-	-
<i>Ancylostoma</i> spp.	-	-	-	-	-
Positive	99a	31b	1b	1b	0b
Effectiveness (%)	0	68.69	98.99	98.99	100
	-	-	-	-	-
<i>Uncinaria</i> sp.	-	-	-	-	-
Positive	19a	2b	2b	0b	0b
Effectiveness (%)	0	89.48	89.48	100	100
	-	-	-	-	-
<i>Trichuris</i> spp.	-	-	-	-	-
Positive	32a	4b	4b	0b	0b
Effectiveness (%)	0	87.5	87.5	100	100
	-	-	-	-	-
<i>Strongyloides stercoralis</i>	-	-	-	-	-
Positive	23a	8b	1b	0b	0b
Effectiveness (%)	0	65.22	95.66	100	100

Note: *Two-tailed Fisher's exact test, different literals in the same row of the same nematode indicate statistical significance $p < 0.05$

Table 2. Effectiveness and persistence of the combination of Moxidectin 3.5g/ Praziquantel 10.0g to treat dogs with cestodes.

	Start	Days After Treatment			
	0	7	14	28	35
<i>Dipylidium</i> spp.	-	-	-	-	-
Positive	104a	26b	0b	0b	0b
Effectiveness (%)	0	75	100	100	100
	-	-	-	-	-
<i>Taenia</i> spp.	-	-	-	-	-
Positive	74b	7c	2c	0c	0c
Effectiveness (%)	0	90.55	97.3	100	100

Note: *Two-tailed Fisher's exact test, different literals in the same row of the same cestode indicate statistical significance $p < 0.05$

Table 3. Effectiveness and persistence of the combination of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g to treat dogs with ectoparasites.

	Days After Treatment (effectiveness)			
	0	7	14	30
<i>Linognathus setosus</i>	-	-	-	-
Positive	6	1	0	0
Effectiveness (%)	0	83.3	100	100
<i>Ctenocephalides felis</i>	-	-	-	-
Positive	28	5	1	0
Effectiveness (%)	0	82.1	96.4	100
<i>Sarcoptes scabiei</i>	-	-	-	-
Positive	9	2	1	0

(Table 3) contd....

<i>Linognathus setosus</i>	Days After Treatment (effectiveness)			
	0	7	14	30
-				
Effectiveness (%)	0	77.7	88.8	100
<i>Ctenocephalides canis</i>	-	-	-	-
Positive	5	1	0	0
Effectiveness (%)	0	80	100	100
<i>Amblyomma americanum</i>	-	-	-	-
Positive	6	1	0	0
Effectiveness (%)	0	83.3	100	100
<i>Dermanyssus hirundinis</i>	-	-	-	-
Positive	1	0	0	0
Effectiveness (%)	0	100	100	100
<i>Demodex canis</i>	-	-	-	-
Positive	5	3	1	0
Effectiveness (%)	0	40	80	100
<i>Demodex injai</i>	-	-	-	-
Positive	4	2	2	0
Effectiveness (%)	0	50	50	100
<i>Ixodes spp.</i>	-	-	-	-
Positive	7	0	0	0
Effectiveness (%)	0	100	100	100
<i>Rhipicephalus sanguineus</i>	-	-	-	-
Positive	9	1	0	0
Effectiveness (%)	0	88.8	100	100
<i>Dermacentor reticulatus</i>	-	-	-	-
Positive	4	1	0	0
Effectiveness (%)	0	75	100	100

Note: *Two-tailed Fisher's exact test, different literals in the same row indicate statistical significance $p < 0.05$

Table 4. Comparison of the pruritus scale and lesion score in dogs that tested positive for ectoparasites and treated with Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0 g.

-	Day 0	Day 7	Day 14	Day 30	SEM
Pruritus	6.26 ^a	2.61 ^b	0.15 ^c	0.03 ^c	0.15
Lesions	407.40 ^a	276.45 ^b	44.87 ^c	2.57 ^c	12.75

Note: ^{abc} Row with different literals presents a significant difference, Tukey's studentized range test, SEM= Standard error of the mean, $\alpha < 0.05$

3.4. Effectiveness of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g Against Ectoparasites

In the study, 83 dogs tested positive for 11 species of ectoparasites: *Linognathus setosus*, *Ctenocephalides felis*, *Sarcoptes scabiei*, *Ctenocephalides canis*, *Amblyomma americanum*, *Dermanyssus hirundinis*, *Demodex canis*, *Demodex injai*, *Ixodes spp.*, *Rhipicephalus sanguineus*, and *Dermacentor reticulatus*. The effectiveness and persistence of the treatment with Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g against ectoparasites in dogs are presented in Table 3. The treatment proved its effectiveness in all the ectoparasites from day 7 AT, until reaching 100% effectiveness by day 14 AT in the *L. setosus*, *Ct. Canis*, *A. americanum*, *Ixodes spp.*, *R. sanguineus* and *D. reticulatus* species. The only specimen of *D. hirundinis* identified in a dog was eliminated by day 7 AT. The treatment reached 100% effectiveness by day 30 AT in all the species of ectoparasites found in dogs.

3.5. Evaluation of Pruritus and Lesions

The pruritus scale decreased from 6.26 to 2.61 between days 0 and 7 AT with a significant difference; likewise, it significantly decreased from day 7 to 14 AT from 2.61 to 0.15. In the evaluations between day 14 to day 30 AT, there was no significant difference in pruritus although by day 30 AT the average pruritus scale was 0.03 taking into account that the range of the visual analogical scale goes from 0 "no itching, no scratching" to 10 "severe itching, constant scratching, chewing, rubbing or licking", the average scale of lesions at the beginning of the study was 407.40 and it significantly decreased by day 7 AT to 276.45, afterward, by day 14 AT it decreased to 44.87 with a significant difference. Between day 14 and day 30 AT there was a decrease in injuries from 44.87 to 2.57 in the score although there was no significant difference (Table 4). Due to these results, we established a positive correlation ($r = 0.7430$, $p = < 0.0001$) between the pruritus scale and the lesions scale.

4. DISCUSSION

A single product that can treat and prevent all the range of taxa of ectoparasites and enteroparasites that affect dogs is not available, consequently, the use of antiparasitic drugs combinations will remain the best therapeutic and preventive solution for many years [6], therefore, it is important to evaluate the effectiveness of new existing formulations in the market. In the study, there were dogs that tested positive for five genera of nematodes: *Toxocara canis*, *Ancylostoma caninum*, *Uncinaria* sp., *Trichuris vulpis*, and *Strongyloides stercoralis* agreeing with what Alvarado-Esquivel *et al.* [15] reported, who mention that the parasites stated before were also more prevalent in their study; however, they did not report *Toxocara canis* that we found and they reported *Giardia canis*, which was not found in this study. In addition to the dog's health problems, the feces represent a significant zoonotic threat because humans who ingest larvae eggs of *Toxocara* sp. can develop visceral or ocular larva migrans [16]. The viable survival of larvae *Ascaris* eggs can remain for several years in the environment; for this reason, prevention and immediate elimination of patent infections are important measures to minimize the risk of zoonotic transmission [17]. Likewise, *Ancylostoma* spp. has a zoonotic potential [18], this is why the opportune treatment of the infection is essential to reduce the negative effects in the host, as well as minimize the risk of environmental contamination with worm eggs that can lead to the zoonotic transmission [17].

Some animals tested positive for two genera of cestodes: *Dipylidium caninum* and *Taenia* spp. The presence of *Dipylidium caninum* in the dogs of this study has been previously reported as a zoonosis in children [19]; therefore, it is a parasite that must be controlled to avoid public health problems. The species of *Taenia* in domestic dogs can cause cysticercosis and coenurosis in a wide range of intermediary hosts, including humans. Mostly, *Taenia* in dogs is distributed at a worldwide level, but some species transmitted by wildlife can be specific to certain regions. Overall, there is little information about the composition and frequency of the species in most regions around the world, making risk strategies and control evaluation difficult [19].

The study identified 11 species of ectoparasites, such as, the ectoparasite *L. setosus*, which is a sucking louse, spends its entire life in the host, and some species cannot survive more than a few days outside the host [20]. Therefore, lice transmission takes place by direct contact. Nevertheless, contaminated brushes, combs, and different materials also influence the contagion [21]. In addition to causing pediculosis in dogs, *L. setosus* is also important in terms of being a vector of *Dipylidium caninum*, an endoparasite found in this study. *Rickettsia felis* is an obligate intracellular Gram-negative bacterium that causes spotted fever transmitted by fleas to humans. In the last decades, *R. felis* has been detected worldwide in fleas of *Ct. felis* and *Ct. canis* [22], both ectoparasites observed in this study; therefore, their control is important for public health. Canine scabies (*Sarcoptes scabiei*) is an intensely itchy and transmissible skin disease of dogs caused by the mite *Sarcoptes scabiei* [23]. This ectoparasite was also found in this study. It is important to have good

pharmacological management of this parasite since the clinical presentation is characterized by pruritus and severe scratching, alopecia, inflammation, excoriation, and hyperkeratosis, potentially associated with secondary bacterial infection and pyoderma. The disease is diagnosed at a worldwide level and can affect dogs of all breeds, age, and gender. The infestation is highly contagious in humans and can develop skin lesions after being in contact with an infested host [24]. In this study, a dog tested positive for *Dermanyssus hirundinis* (a bird mite), even though this parasite is found in birds like pigeons, some dogs with hunting habits can become infested with this louse. Molecular studies have demonstrated that the different species of *Dermanyssus* can adapt to different hosts [25]. We also found *D. canis* and *D. injai* mites, the control of these mites is important since they come from outer sources on the mammals' skin [26], which cause inflammatory disease of the skin when the population of these parasites surpasses the balance point. In this research, we also found ticks, in previous years it was not a common question to find this type of ectoparasites; nevertheless, they are now present and preventive management of these parasites should be carried out since in addition to causing health problems in patients they are also vectors of multiple diseases for humans [27]. This study demonstrated that the treatment with Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g was also effective to decrease lesions associated with pruritus in dogs that were positive for ectoparasites. This result is important because the *L. setosus* are very active lice and a severe infestation can cause acute irritation and fragile skin with erythema, peeling, scabs, papules, and pruritus, similar to the way of mite *S. scabiei*. The pruritus and the associated scratching cause traumatic damage to the skin that includes alopecia and secondary bacterial infection (pyoderma) [28].

The treatment had significant effectiveness from day 7 AT against the five nematodes analyzed (average effectiveness of $\geq 77.25\%$) having greater effectiveness to treat *Uncinaria* sp. (89.48%) and *Trichuris* spp. (87.5%). The effectiveness of Moxidectin/ Praziquantel was $\geq 99.8\%$ from day 14 to day 35 AT on all the nematodes analyzed. This result was better compared to one presented in a previous study that demonstrated the effectiveness of $>95\%$ of the combination of Emodepside plus® tablets of Praziquantel against *Uncinaria* sp. in dogs [29]. The use of this combination for the parasite *Strongylus* spp. had no side effects in these patients, as they would have with the use of Ivermectin or the anthelmintic resistance of Fenbendazole, commonly used treatments for this parasite [30].

The effectiveness and persistence of the treatment with Moxidectin 3.5g/ Praziquantel 10.0g on the intestinal cestodes in dogs showed a significant difference in the effectiveness against *Dipylidium* spp. and *Taenia* spp. (effectiveness of 82.7%) from day 7 AT. The effectiveness of Moxidectin/ Praziquantel had 100% effectiveness from day 14 AT in the case of *Dipylidium caninum* until day 35; in the case of *Taenia* spp. it reached 100% effectiveness by day 28 and day 35 AT. This would not be possible if the "transmitter reservoir" flea is not eliminated at the same time. This result is related to Praziquantel which has been described as an anthelmintic agent with activity against a broad spectrum of trematodes and

cestodes [31]. This result agrees with what Charles *et al.* [32] reported, who said that the topical solution of Emodepside/Praziquantel turned out to be safe and highly effective against infections by *D. caninum* and *T. taeniformis* in cats that are easily stressed and more sensitive to antiparasitic drugs. In several studies, Praziquantel has been safe and effective in oral and topical presentations [33]. The treatment with Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g proved its effectiveness in all ectoparasites from day 7 AT, until reaching 100% effectiveness by day 14 AT in the *L. setosus*, *Ct. Canis*, *A. americanum*, *Ixodes* spp., *R. sanguineus*, and *D. reticulatus* species. The only specimen of *D. hirundinis* identified in a dog was eliminated by day 7 AT. The treatment reached 100% effectiveness by day 30 AT in all the species of ectoparasites found in dogs. These results are important since it was possible to have proper control of these ectoparasites with zoonotic potential, which agrees with what Krüdwagen [7], reported, where they tested the effectiveness and safety of the topical spot-on application of Imidacloprid/ Moxidectin in dogs with these ectoparasites. In addition, Petersen *et al.* [34] showed that Imidacloprid/ Moxidectin applied topically every month during the study of 84 days did not reach the proportion of mite-free dogs required to prove good effectiveness; however, the use of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g in this study has a high concentration of Moxidectin (3.5%), which presents the product as a good choice for this pathology since the results of this study show that it eliminates 100% mites and contributes to the elimination pathway of these ectoparasites. The effect of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g against ticks is associated with the high concentration of Moxidectin (3.5%), considering that other studies in which the concentration was of 2.5% did not have this effect. These results are also related to the function of Imidacloprid, which is a neonicotinoid insecticide that acts as a strong agonist of the nicotinic acetylcholine receptors in the postsynaptic membrane causing the sustained depolarization of the neuron and death of the flea, louse or tick [33, 34].

CONCLUSION

The application of Moxidectin 3.5g/ Praziquantel 10.0g applied topically was effective to treat nematodes (*Toxocara canis*, *Ancylostoma caninum*, *Uncinaria* sp., *Strongyloides stercoralis*, and *Trichuris vulpis*) and cestodes (*Dipylidium caninum* and *Taenia* sp.). A single topical treatment of Imidacloprid 10.0g/ Moxidectin 3.5g/ Praziquantel 10.0g was also safe and highly effective to treat ectoparasites like *L. setosus*, *Ct. felis*, *S. scabiei*, *Ct. canis*, *A. americanum*, *D. hirundinis*, *D. canis*, *Ixodes* spp., *R. sanguineus*, *D. injai*, and *D. reticulatus* in parasitized dogs. It was also a useful treatment to control pruritus and decrease lesions.

LIST OF ABBREVIATIONS

AT = After the Treatment

COMECYT = Chair at the Mexican Council of Science and Technology

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical review and approval for this study were waived, as

the owners of the animals signed an informed consent where they agreed that the different treatments can be administered to the animals.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The authors agree that the data provided in the publication, including the relevant raw data, will be freely available to any researcher who wants to use these for non-commercial.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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