Pharmacokinetics of the Slow-release Drug in the Form of Moxidectin-based Solution for Dogs and Cats

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ABSTRACT

The pharmacokinetic characteristics of the moxidectin-based drugs have been studied in the blood serum of animals after a single oral administration of the drug at the therapeutic dose in form of syrup. The drug is intended to control parasitic diseases of cats and dogs. The present studies on cats and dogs (drug administration and blood sampling) were conducted in the experimental farm of Kurilovo, Russia, for three months. The study involved six dogs and six cats, half breed, aged one to four years. The samples included six dogs (four male and two female) and six cats (three male and three female), and groups were formed according to the principle of analog groups. The drug, moxidectin, was orally administered once at the dose of 1.5 mg per one kg of animal's weight. The active substance of the drug was identified in the blood serum of animals by High-Performance Liquid Chromatography (HPLC) with fluorescence detection. The result of the current study showed that based on the pharmacokinetics of moxidectin, the concentration of the active substance in the blood serum after three hours reached 134.80-498.09 ng/ml in cats and 479.07-1459.40 ng/ml in dogs. The obtained results indicated that a single administration of the drug at the recommended therapeutic dose could ensure the maintenance of therapeutic concentrations of moxidectin in the blood, and accordingly, the protection of animals from parasites for up to 90 days.

Keywords: Cats, Dogs, Moxidectin, Pharmacokinetics, Solution

INTRODUCTION

Numerous studies have been performed on a comparative assessment of the pharmacokinetics of various macrocyclic lactones. Macrocyclic lactones are natural avermectins produced by soil actinomycetes of the species *Streptomyces avermitilis*, and they are structurally similar to milbemycins (produced by *Streptomyces hygroscopicus*) that possess a wide spectrum of both nematicidal and insectoacaricidal activities. The most widespread macrocyclic lactones are kindred; natural products include avermectin B1a and B1b, aversect-1, doramectin, milbemectin, as well as milbemycins A3 and A4, and semi-synthetics are also used in products, such as ivermectin, eprinomectin, selamectin, lepimectin, and moxidectin which are a nemadectin derivative (Platonova and Avsevieva, 2018; Jafarov et al., 2019).

The study on the effect of their pharmacokinetics on fat deposition in pigs showed an increased resistance of moxidectin in the plasma of pigs having a normal diet, compared to those having a diet with an increased linoleic acid content, while there were no differences in the pharmacokinetic of ivermectin among animals receiving maintenance or normal ration (Craven et al., 2002). The decreased rate of fat deposition affected the pharmacokinetic location of highly lipophilic drugs like moxidectin, but did not affect the pharmacokinetic location of the less lipophilic drugs, such as ivermectin. Given the pharmacokinetic parameters for the parent molecules, the persistence of doramectin and moxidectin is significantly longer than that of ivermectin, which may positively influence their efficacy after subcutaneous injection, associated with an interval among doses (Oukessou et al., 1999; Sallovitz et al., 2003; McCall, 2005; Al-Azzam et al., 2007; Gokbulut et al., 2010).

The pharmacokinetics of moxidectin was proportional to the doses used in previous studies (3 to 36 mg per person) and a long half-life was noted on average as 20-35 days. Thus, the results have shown that moxidectin is safe and well-tolerated by the body at doses ranging from 0.05 to 0.6 mg/kg. It is noted that moxidectin in liquid dosage form reaches its maximum concentration in blood plasma faster than tablets by 0.9 hours (Cotreau et al., 2003, Korth-Bradley et al., 2012). Regarding a recent study on the pharmacokinetics of moxidectin in Gelmintal Syrup on cats and dogs at single administered at a dose of 0.3 mg/kg, it was found that the maximum moxidectin concentration in blood of cats reached 9.3 ng/ml after 3 hours of drug administration, dropped to 3.0 ng/ml by 24 hours, and remained at 1-3 ng/ml up to 720 hours (Arisov et al., 2016a). In another study addressing the effect of the drug on dogs, a similar procedure was observed. The maximum concentration was reached three to six hours after the administration (once at a dose of 0.3 mg/kg) (75.1 ng/ml), and by 24 hours, it decreased to 12-16 ng/ml and remained in the range of two to five ng/ml

throughout the study (Arisov et al., 2016b). Although many studies on the pharmacokinetics of moxidectin have been conducted worldwide, the presence of this substance in therapeutic concentrations in the serum of domestic carnivores for such a long time as 90 days has not been studied. The present study aimed to investigate the pharmacokinetics of moxidectin in the blood serum of dogs and cats after a single application of the drug "Neoterica Protecto syrup" at the recommended therapeutic dose of 1.5 mg/kg for 90 days.

MATERIALS AND METHODS

Ethical approval
When the experiment was being designed, the involved researchers were guided by the principles of humane treatment of experimental animals according to the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (ETS 123). Animal handling was controlled according to directive 2010/63/EU of the European Parliament and the European Union Council dated 22 September 2010 on the protection of animals used for scientific purposes.

Experimental groups
The experiment involved six mongrel dogs (four males and two females) aged one to five years weighing 9.3-14.7 kg, and six mongrel cats (four males and two females) aged one to five years weighing 1.5-4.5 kg. The animals were kept in nursery conditions, and had not received any chemotherapeutic drugs (30 days before the study), and were clinically healthy (Guidelines for the examination of medicines, 2013).

Sample collection
To study the pharmacokinetics of moxidectin in the body of cats and dogs after the administration, the drug was individually administered orally in a single dose of 1.5 mg per one kg of animal's weight. Blood samples were collected from the internal femoral vein or the anterior saphenous vein of the forearm with sterile needles directly into special tubes. Two ml of blood samples from the cats and 2-5 ml from the dogs were taken before the drug administration, and this procedure was repeated after 3, 6, 12, and 24 hours as well as 3, 6, 10, 20, 45, 60, 75, and 90 days. At each study period, blood samples were taken from six cats and six dogs (Guidelines for the examination of medicines, 2013).

Blood samples were collected in cipher-marked polymeric disposable tubes without a coagulation activator. At least 1 ml of the serum samples was separated and taken into cipher-marked Eppendorf tubes, and the serum samples were frozen. All samples were stored in a freezer at a temperature of -30°C until the initiation of the study. The main parameter that was identified during the study was the moxidectin content in the blood serum. The pharmacokinetic parameters of the active substance in the body of cats and dogs were calculated (using the PKSolver - a program that includes a formula for calculating) based on the obtained results (Alvinerie M. et al., 1995, Zhang Y. et al., 2010).

Methodology of experiment
The concentrations of moxidectin in the serum samples of cats and dogs were measured using a validated technique. The stability and correctness of the measurements were monitored by adding them to the analytical run of calibration standards for comparison and blank samples of bioactive matrices, and control samples were prepared based on blood serum free of any analyte. The analyte and internal standards were identified by comparing the peak retention times of these components. To determine the retention times, the obtained extracts were processed according to the procedure for preparing blood serum samples containing specified concentrations of moxidectin and internal standards.

When obtaining calibration graphs for moxidectin, linear interpolation with an intercept was used (y: kx+b) with the balance 1/x depending on moxidectin concentration (C_{Mox}) in blood. To calculate the concentrations in the studied blood serum samples, the equations obtained for the trend line of the calibration graphs were utilized by extracts of the blood serum sample model:

$$C_{Mox}: \frac{\frac{S_{Mox}}{S_{IS}} - b}{k},$$

Where, k is a slope coefficient of the calibration function and b denotes an intercept of the calibration function.

Equipment
The utilized pieces of equipment in the current study included Shimadzu AUW220D laboratory balance (Shimadzu, Japan), Shimadzu LC-20 Prominence chromatographic system (Shimadzu, Japan), Kromasil 100-3.5-C8 chromatographic column 3.0 x 150 mm (Nouryon, Netherlands), Kromasil 100-3.5-C8 pre-column 2.1x10 mm (Nouryon, Netherlands), Biosan Vortex V-1Plus Vortex (BioSan, Latvia), SNOL 58/350 low-temperature electric oven (drying oven) (SNOL-THERM, Russia), SNOL 7.2/900 laboratory electric furnace (muffle furnace) (SNOL-THERM, Russia), Sartorius mechanical dispensers (Sartorius AG, Germany), Eppendorf 5418 centrifuge (Eppendorf, Germany).

Statistical analysis

The results were statistically processed using Microsoft Excel, 2013. The Descriptive statistics of the obtained data included finding the mean values, and relative standard deviations from the mean, and standard errors in Microsoft Excel. The pharmacokinetic parameters were calculated using the PKSolver program (add-in for Microsoft Excel) (Zhang et al., 2010). Figures were made using MS Excel and Shimadzu LabSolutions programs.

RESULTS

The results of studying the pharmacokinetics of moxidectin in the blood serum of cats and dogs have shown that moxidectin is rapidly absorbed from the gastrointestinal tract, and its concentration reaches its maximum values by three hours in both cats and dogs. Maximum moxidectin concentrations in the serum ranged from 136.211 to 467.116 ng/ml in cats and 491.861 to 1370.217 ng/ml in dogs. Then, the active substance concentration in the blood serum of animals decreased and was determined by 90 days after the administration in the range of 1.310-2.603 ng/ml and 1.268-2.821 ng/ml in cats and dogs, respectively. Moxidectin concentrations were identified in the blood serum of all animals on day 90 and were above the lower limit of quantitative determination (1 ng/ml).

The pharmacokinetic parameters of moxidectin were calculated using the PKSolver (Zhang et al., 2010), and are presented in tables 1 and 2. Changes in the moxidectin concentration in the cats involved in the experiment are shown in Figure 1. The figure shows the mean values of observed concentrations and interpolation lines obtained as a result of applying the model hypothesis of the moxidectin distribution using an approximant in the approximation of a two-compartment model of the active substance distribution. In addition, marked confidence intervals (CI = 0.95) characterized the variability of individual concentrations.

The volume of distribution is a hypothetical volume of body fluid required to evenly distribute the entire administered dose at a concentration similar to that in blood plasma. High volume of distribution indicated that a drug actively penetrates into biological fluids and tissues. If a drug is actively bound, for example, by adipose tissue, its concentration in the blood can almost instantly become very low, and the volume of distribution will reach several hundred liters, and exceed the actual amount of body fluids. In this regard, it is also called as apparent Volume of Distribution (Vss). In the present study, Vss averaged 0.0972 ng/ml in cats, and 0.019428 ng/ml in dogs. Total body clearance is the amount of plasma or blood that is completely cleared of a drug in a time unit. Due to the fact that the main excretion routes are the kidneys and the liver, and the total body clearance is the sum of renal and hepatic clearance. The main physiological factors that determine clearance are functional state of the main physiological systems of the body, blood supply volume, and blood velocity in the organ. As a result of the studies, CL averaged 0.000093 (ng/ml)/h in cats, and 0.000084 (ng/ml)/h in dogs. A half-life is the time required to reduce the drug concentration in plasma by 50%. Fifty percent of a drug is excreted from the body in almost one half-life period, 75% in two periods, and 87% in three periods, etc. In the current study, the half-life ($t_{1/2}$) averaged 935 hours (39 days) in cats, and 1096 hours (45 days) in dogs.

Table 1. Pharmacokinetic parameters of moxidectin in the blood serum samples of cats after a single oral administration of the drug at a dose of 1.5 mg/kg within 90 days

Parameter	Cat number						Mean	RSD (%)
	1	2	3	4	5	6		
$t_{1/2}$, h	1548.241	737.2329	1113.7695	645.8868	416.9375	1148.7031	935.128	43.95
Tmax, 1/h	3	3	3	3	3	3	3	0
Cmax, ng/ml	136.211	289.563	467.116	405.359	376.221	168.924	307.232	43.33
C_0, ng/ml	0	0.018	596.61265	0.065	0.054	0.040	0.0378	64.49
Clast /Cmax	0.01082	0.006613	0.0028515	0.006421	0.003817	0.007754	0.00637	44.71
AUC $_{0-t}$, ng/ml *h	8608.841	12904.37	20845.367	20882.20	20797.35	8964.15	15351.2	38.38
AUC$_{0-inf}$, ng/ml *h	11901.22	14941.17	22985.664	23307.73	21661.13	11135.119	17506.2	31.34
AUC $_{0-t}$ /0-inf	0.72335	0.863678	0.9068855	0.895935	0.960123	0.805034	0.0835	9.72
AUMC 0-inf, ng/ml *h^2	1941475	1334016	15238669	1680769	1017160	13441464	1473572	21.65
MRT, h	1631.323	892.8460	662.96405	721.1209	469.5784	1207.1235	935.3	44.93
Vz,(ng/ml)	0.281522	0.106779	0.1048586	0.059968	0.041654	0.223243	0.1370	69.25
CL, (ng/ml)/h	0.000126	0.000100	0.000065	0.000064	0.000069	0.000134	0.000093	33.34
Vss, (ng/ml)	0.205607	0.089636	0.0432637	0.046408	0.032517	0.162610	0.0972	73.25

RSD: Relative standard deviation; $t_{1/2}$: Drug elimination time from the body by biotransformation and excretion of 1/2 of the administered or received and absorbed dose; T_{max}: Time to reach the maximum concentration of the active substance; C_{max}: Active ingredient maximum concentration; Clast: last measured concentration of a substance; AUC$_{0-t}$: Area under the curve "active substance concentration-time" in the time frame from 0 to the moment (t) of the last biomaterial sampling; AUC$_{0-inf}$: Area under the curve "active substance concentration-time" in the timeframe from 0 to ∞; AUMC$_{0-inf}$: Area under the curve "product of time and drug concentration"; MRT: The average substance retention time in the systemic circulation; Vz: Distribution volume - the ratio of the total content of a substance in the body to its serum concentration; CL: Clearance or extraction coefficient - an indicator of the of a substance excretion rate from the body; V_{ss}: apparent volume of distribution at equilibrium.

Table 2. Pharmacokinetic parameters of moxidectin in the blood serum samples of dogs after a single oral administration of the drug at a dose of 1.5 mg/kg within 90 days

| Parameters	Dog number						Mean	RSD (%)
	1	**2**	**3**	**4**	**5**	**6**		
$t_{1/2}$ (h)	957.773	1703.632	1508.1140	1343.670	462.827	599.555	1095.928	45.93
Tmax (1/h)	3	3	3	3	3	3	3.0	0
Cmax (ng/ml)	887.536	1058.026	1129.64	1370.217	521.31	491.861	909.765	38.34
Clast /Cmax	0.001428	0.001901	0.0022219	0.001577	0.004120	0.005735	0.002830	60.92
AUC $_{0-t}$ (ng/ml*h)	28585.27	34217.60	42851.047	38523.5	33635.9	44936.0	37124.88	16.57
AUC$_{0-inf}$ (ng/ml*h)	30337.36	39162.73	48312.176	42712.64	35070.16	47376.10	40495.19	17.38
AUC $_{0-t}$ /0-inf	0.942246	0.873728	0.8869616	0.901923	0.959103	0.948495	0.91874	3.88
AUMC 0-inf (ng/ml*h^2)	13025019	31274176.1	34442217	26415797.8	19667710.9	27823896.3	25441469	30.90
MRT (h)	429.3392	798.5696	712.90966	618.4538	560.8104	587.2981	617.896	20.65
Vz, (ng/ml)	0.068320	0.094138	0.0675528	0.068077	0.028559	0.027386	0.059005	44.21
CL (ng/ml)/h	0.000049	0.0000383	0.000310	0.0000351	0.0000427	0.0000316	0.000084	130.9
Vss (ng/ml)	0.021228	0.030586	0.0004596	0.021719	0.023986	0.018594	0.019428	52.19

RSD: Relative standard deviation; $t_{1/2}$: Drug elimination time from the body by biotransformation and excretion of 1/2 of the administered or received and absorbed dose; T_{max}: Time to reach the maximum concentration of the active substance; C_{max}: Active ingredient maximum concentration; Clast: last measured concentration of a substance; AUC_{0-t}: Area under the curve "active substance concentration-time" in the time frame from 0 to the moment (t) of the last biomaterial sampling; AUC_{0-inf}: Area under the curve "active substance concentration-time" in the timeframe from 0 to ∞; $AUMC_{0-inf}$: Area under the curve "product of time and drug concentration"; MRT: The average substance retention time in the systemic circulation; Vz: Distribution volume - the ratio of the total content of a substance in the body to its serum concentration; CL: Clearance or extraction coefficient - an indicator of the of a substance excretion rate from the body; V_{ss}: apparent volume of distribution at equilibrium.

Bioavailability is the part of a drug dose that reaches systemic blood after its extravascular injection. The bioavailability can be absolute and relative, and is defined as the ratio of Area Under Curve (AUC) values. The area under the concentration time curve is an integral parameter proportional to the total amount of a drug in the systemic blood (Kukes, 2009). The maximum concentration characterizes efficacy and safety of a drug, and its values should not go beyond a therapeutic range. The time-to-peak concentration with a "concentration - effect" linear relation allows to estimate the time of the maximum effect of a drug (Belolipetskaya and Sukhanov, 2005). The present study found that time to reach the maximum concentration of the active substance in all animals was 3 hours, and active ingredient maximum concentration of moxidectin averaged 307.232 ng/ml in cats, and 909.765 ng/ml in dogs.

One of the main factors that determines the effect of a drug is its concentration in the receptor area. Such concentration is determined rather difficult, therefore, in practice, drug concentration values in the blood plasma are used to describe processes that occur with such drug in the body. The movement of a drug in the body is usually depicted as a concentration time curve which is the dependence of the concentration of a drug or its metabolite in blood plasma on the time after drug administration.
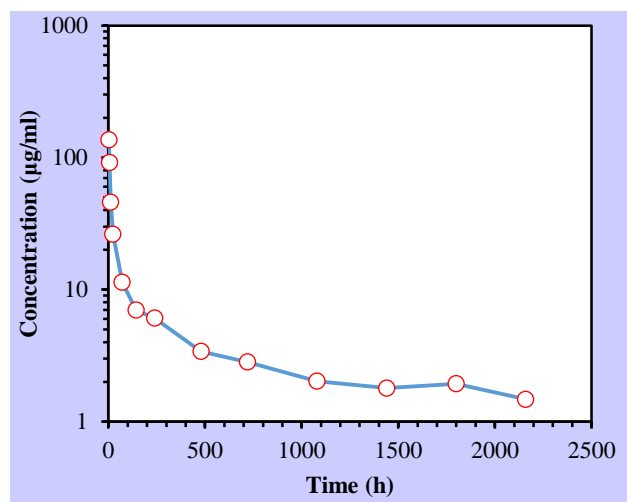
Figure 1. Dynamics of changes in the moxidectin concentration in the blood serum of the cats as a result of oral administration of the drug "Neoterica Protecto syrup" at a dose of 1.5 mg/kg
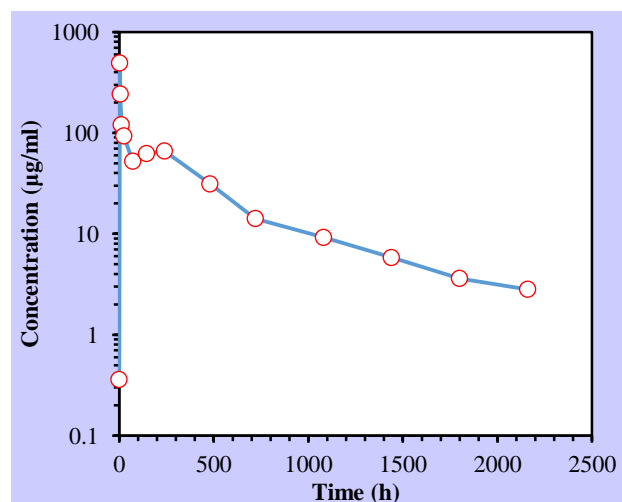
Figure 2. Dynamics of changes in the moxidectin concentration in the blood serum of the dogs as a result of oral administration of the drug "Neoterica Protecto syrup" at a dose of 1.5 mg/kg

DISCUSSION

According to the literature, when studying the metabolism of moxidectin in various animal species after quantitative determination by HPLC, the 14C-moxidectin metabolism was the highest in the liver microsomes of sheep (32.7%), compared to cows (20.6%), deer (15, 4%), goats (12.7%), rabbits (7.0%), and rats (3.0%) while the smallest amount in metabolism occurred in microsomes of pigs, that is 0.8% of the total amount of detected metabolites (Dupuy et al., 2001). When studying the moxidectin distribution in tissues of cattle after a single subcutaneous administration, the highest content of the residues was found in the abdominal fat and the back, and the lowest content was found in the liver, kidneys, and muscles of the coupling (Zulalian et al., 1994).

Pharmacokinetic studies of moxidectin and ivermectin in horses showed a longer time for moxidectin presence, as demonstrated by a fourfold increase in mean values of the time, compared to ivermectin and longer time and higher concentrations of moxidectin, compared to ivermectin explain the longer anthelminthic effect of drug Equest (moxidectin) (Perez et al., 1999).

When studying the comparative kinetics of macrocyclic lactones 80 days after treatment of cattle, metabolites were found in the plasma as 5.75% of doramectin, 8.50% of ivermectin, and 13.8% of moxidectin of the total amount of their respective parent drugs excreted in plasma (Lanusse et al., 1997).

The studies by Belykh (2020) have indicated that moxidectin after being applied externally in the form of a solution is well absorbed into the systemic circulation of animals and reaches a maximum concentration after 4-10 days, and it also reaches significant concentrations of moxidectin in the blood serum of cats and dogs determined within 28 days after a single application. Regarding the pharmacokinetics of the active substances of Gelmintal Tablets (praziquantel and moxidectin) after oral administration, it was found that moxidectin remained in the blood of animals for 25 days (Arisov et al., 2016b).

Based on literature data of other authors and on the current research, it can be concluded that a lipophilic substance, moxidectin, reaches its maximum concentration at three hours after being administered orally in a high dose of 1.5 mg/kg, and begins to accumulate in adipose tissues of the animal body in large quantities, which explains the low level of apparent volume of distribution (Vss). Subsequently, considering a high level of metabolism in the liver, moxidectin is gradually released from fat depot into the blood plasma of animals, which ensures that the drug concentrations maintained at a therapeutic level for such a long time (up to three months).

The present study has confirmed the long-term presence of moxidectin in the blood serum of animals after a single oral administration of Neoterica Protecto Syrup in the minimum therapeutic dose (1.5 mg of moxidectin per 1 kg of animal weight). The results of this study showed that moxidectin was rapidly absorbed into the blood of animals after three to six hours reaching the maximum concentrations, and was found by the end of the experiment in the blood serum of animals, which indicates its long-term therapeutic effect up to 90 days. Based on the results obtained, it can be concluded that the maintenance of therapeutic concentrations of moxidectin for 90 days should ensure the protection of animals from ectoparasites and nematodes. To confirm this hypothesis, further clinical studies of the drug "Neoterica Protecto syrup" are needed when used for the treatment and prevention of parasitosis of cats and dogs on target animal species for 90 days. However, given that a therapeutic dose of moxidectin is quite high compared to other similar drugs used for animals, studies of toxicological properties of the drug and its tolerance in target animal species at increased therapeutic doses are necessary. Furthermore, allergic reactions, severe renal failure, and acute liver disorders are listed as contraindications of moxidectin. When studying the efficacy, the drug must not be used for depleted, sick, or infected animals, as well as animals weighing less than 2.0 kg. Consideration should be given to the poor tolerance of collies, bobtails, Shetland sheepdogs, and other breeds that are sensitive to macrocyclic lactones, and treatment of animals should be supervised by a veterinarian.

CONCLUSION

The study of pharmacokinetics is mainly based on the assessment of the active substance concentration at certain points in time after the application of the drug. Blood is the main object of research. The study of the drug concentration in the blood provides information on the drug circulation time in the body, drug bioavailability, the effect of concentrations on the pharmacological effect, therapeutic and lethal dosage, and the dynamics of active or toxic metabolites formation.

As a result of moxidectin pharmacokinetics study after a single use of an antiparasitic drug in syrup form at a therapeutic dose of 1.5 mg moxidectin per one kg of animal weight, it was found that active substance concentration in the blood serum has respectively reached levels of 136.211 - 467.116 ng/ml and 491.861-1370.217 ng / ml in cats and dogs in three hours. The active substance remained present in the blood circulation of both species for at least 90 days after the single oral administration of the drug. The findings indicated that a single administration of the drug at the recommended therapeutic dose ensures the maintenance of therapeutic concentrations of moxidectin in the blood for 90 days. Accordingly, it should provide protection of animals against parasites during this period.

DECLARATIONS

Authors' Contribution

Gulnara B. Arisova and Mikhail V. Arisov planned the study, developed the experimental design, and were directly involved in the experiment. Irina A. Stepanova participated in the interpretation of the results and the writing of the scientific paper. All authors read and approved the final manuscript and analyzed data.

Competing interests

The authors state no conflict of interest.

Acknowledgments

Ethical considerations

Plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been checked by the authors. All the authors approved and agreed to publish the manuscript.

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