Received: 27 September 2022 | Accepted: 23 November 2022

DOI: 10.1111/jvim.16602

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Effects of a single subcutaneous dose of enoxaparin on veterinary viscoelastic coagulation monitor variables in healthy cats: Double blind, placebo controlled cross-over trial

Ivayla D. Yozova[1] | Michael S. Kent[2] | Karl E. Jandrey[2]

[1]Tāwharau Ora-School of Veterinary Science, Massey University, Palmerston North, New Zealand

[2]Department of Surgical and Radiological Sciences, School of Veterinary Science, University of California, Davis, Davis, California, USA

Correspondence
Ivayla D. Yozova, Tāwharau Ora-School of Veterinary Science, Massey University, Private Bag 11-222, 4442 Palmerston North, New Zealand.
Email: i.yozova@massey.ac.nz

Funding information
Center for Companion Animal Health at University of California, Davis, USA; Wenzel Fund for Feline Research at Massey University, New Zealand, Grant/Award Number: RM22764

Abstract

Background: Cats placed on anticoagulant medication require frequent monitoring. The veterinary viscoelastic coagulation monitor (VCM-Vet) could provide a convenient and cost-effective monitoring, enabling therapeutic decision making.

Hypothesis/Objectives: Enoxaparin will lead to changes in VCM-Vet variables and these will correlate with antiXa activity.

Animals: Twenty-one healthy cats.

Methods: Cats were randomized to receive either enoxaparin (1 mg/kg) subcutaneously or 0.9% NaCl (equal volume) and crossed over with a 7-day washout period. The investigators were blinded to group allocation until data analysis. Jugular blood samples were drawn at time 0, and 2, 4, and 8 hours after injection for VCM-Vet analysis within 2 min of collection. Citrated plasma was frozen at −80°C for antiXa activity analysis. A Generalized Linear Model was completed to assess changes between baseline measurements and all time points.

Results: Significant differences between the enoxaparin-treated cats and controls at for T0h and T2h were found and presented as mean ± SD for clotting time (enoxaparin, 593.4 ± 78.0 s; control, 448.5 ± 50.3 s, $P < .001$), clot formation time (enoxaparin, 183.1 ± 41.7 s; control, 155.4 ± 28.0 s, $P = .001$), and alpha angle (enoxaparin, 52.4 ± 6.1°; control, 56.9 ± 3.7 s, $P = .003$). AntiXa activity was significantly different between T0 and all other timepoints for the enoxaparin group ($P < .001$). There was no correlation between changes in clotting time and antiXa activity.

Conclusions and Clinical Importance: The VCM-Vet detects a difference at 2 hours after single-dose enoxaparin administration and it can be useful for anticoagulant therapy monitoring in cats.

KEYWORDS
cage-side, viscoelastic coagulation testing, heparin, point-of-care

Abbreviations: CFT, clot formation time; CT, clotting time; LI, lysis index; LMWH, low-molecular-weight heparin; MCF, maximum clot firmness; UFH, unfractionated heparin; α-A, alpha angle.

1 | INTRODUCTION

Antithrombotic therapy is recommended for use in cats with evidence or at risk of arterial or venous thrombosis.[1] Antiplatelet drugs are currently recommended in cats at risk or as prevention of reoccurrence of arterial thromboembolism.[2,3] Anticoagulants, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and factor Xa inhibitors, are used as monotherapy or in combination with antiplatelet agents in cats at high risk of arterial thromboembolism, for acute crisis and long-term management.[2,4-6] Antiplatelet and anticoagulant administration, especially long term, can be associated with complications such as bruising or bleeding if excessive doses are used or failure to prevent thrombosis in the case of insufficient dosing. Therefore, therapeutic monitoring is required in many cases to ensure optimal doses are administered. The CURATIVE guidelines on antithrombotic use in veterinary patients suggest monitoring the effects of both UFH and LMWH using anti-Xa activity in treated cats, as the current recommendations in people.[7,8] However, panelists acknowledge the considerable knowledge gap in this domain.[7]

Indeed, investigations on the monitoring potential of anti-Xa activity assays in cats is limited to small groups of healthy cats. Depending on the design and drugs used, results vary significantly.[9-12] Further to these discrepant findings, anti-Xa activity might not be ideal for monitoring of anticoagulant therapy, because of cost and availability.

Viscoelastic coagulation testing could present an alternative for monitoring anticoagulant effects; however, studies are limited. Thromboelastography (TEG) is more sensitive to assess heparin-induced anticoagulation than conventional coagulation testing in people.[13-15] There is a correlation between TEG variables and anti-Xa activity in people undergoing orthopedic surgery.[16] Anti-Xa activity is not correlated with TEG tracings after administration of UFH and LMWH in a small group of healthy cats.[12]

The VCM-Vet is a novel point-of-care viscoelastic coagulation monitor (with the potential for wide clinical use).[17] It provides variables similar to TEG and Rotational Thromboelastometry, while it does not require sample manipulation.[17] The device has been validated for use in dogs, cats and mice and reference intervals are established[18-20] with studies in more species underway. The aim of this study was to evaluate whether administration of enoxaparin will result in significant changes VCM-Vet variables and the relationships between those and changes in anti-Xa activity. We hypothesized that a single dose of enoxaparin administered subcutaneously will result in transient hypocoagulable changes detectable by the measured variables of the VCM-Vet and correlate with anti-Xa activity.

2 | MATERIALS AND METHODS

2.1 | Animals

This was a prospective double-blind placebo controlled cross-over experimental trial. The study protocol was approved by the Massey

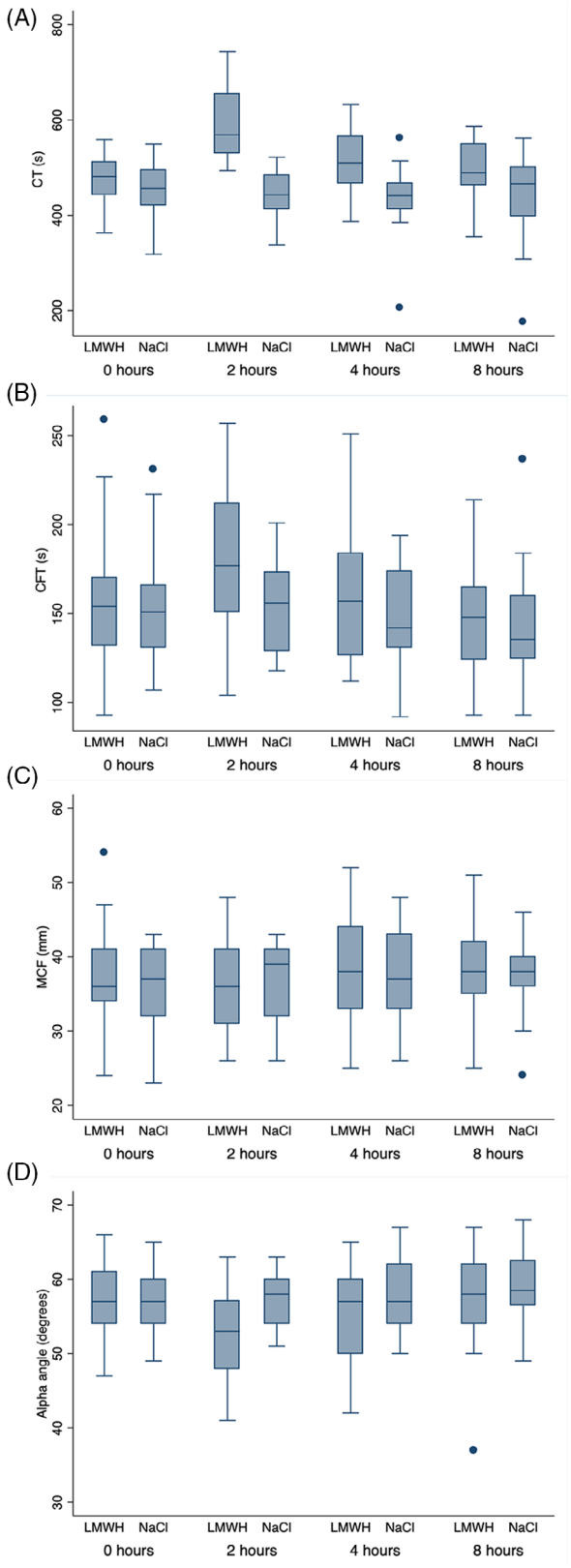

FIGURE 1 Box-and-whisker plots comparing veterinary viscoelastic coagulation monitor variables between low-molecular-weight heparin and 0.9% NaCl groups at T0, T2, T4, and T8. (A) Clotting time (CT). (B) Clot formation time (CFT). (C) Maximum clot formation (MCF). (D) Alpha angle (Alpha). The blue dots represent outliers.

University Animal Ethics Committee (Protocol 19/109). Twenty-one healthy research-purposed cats from the Centre for Feline Nutrition at Massey University, New Zealand were enrolled. Cats were deemed healthy based on physical examination, complete blood count, and biochemistry analysis. Additionally, all cats were negative for occult cardiomyopathy by using the 2 min Screening Echocardiogram for cats.[21]

2.2 | Device

The VCM-Vet (Entegrion, Inc.) uses disposable cassettes analysis. The cassette is warmed to 37°C using a proprietary warming plate. Whole untreated blood (340 µL) is transferred into the cassette well within 2 min after venipuncture. The blood moves from the well via capillary action in between 2 frosted glass plates within the cassette. The cassette is then placed into the VCM-Vet device and analysis begins. As the blood coagulates, the friction detected between the plates as coagulation occurs relates to the clot kinetics which are transmitted to a receiver device. The monitor displays both a graph and series of values for the following viscoelastic clotting variables: Clotting time (CT)—the time from the beginning of the test until the time when the amplitude of 1% is achieved; clot formation time (CFT)—the time between the 1% amplitude and 10% amplitude of the clotting signal; alpha angle (α-A)—the angle between the middle axis and the tangent to the clotting curve through the 1% amplitude point; describes the kinetics of clotting; maximum clot firmness (MCF)—the measure of the firmness of the clot and therefore the clot quality; it is the maximum amplitude that is reached before the clot is dissolved by fibrinolysis; Lysis Index at 45 min after CT (LI45)—represents the fibrinolysis 45 min after CT; measured as the relation of the amplitude to the maximum clot firmness (MCF) (% remaining clot firmness).[18]

2.3 | Procedures

Cats were randomized to receive enoxaparin (Clexane 20 mg/0.2 mL, Sanofi-Aventis New Zealand Ltd, Auckland, New Zealand) 1 mg/kg or 0.9% NaCl (Baxter, New Zealand) equal volume subcutaneously with a 7-day washout period after which the intervention groups were crossed over. The investigators were blinded until data analysis. All cats were handled using Low Stress Handling by a certified research assistant. All jugular blood samples (2 mL) were drawn using a 23-gauge needle at time 0, and 2, 4, and 8 hours after injection by the same investigator (IY) using a vacutainer technique according to the guidelines for viscoelastic testing.[22] Sampling alternated between each jugular vein at each timepoint. Each cat was examined for pain, discomfort, and bruising before and after each venepuncture. Blood was divided into: VCM-Vet test cartridge, cryovial with 4% sodium citrate, and an EDTA or serum separator tube. A CBC, PCV, TP, and manual blood smear were evaluated at time 0 for each cat. Cryovials were frozen at −80°C until shipping for antiXa activity measurements.

TABLE 1 Main viscoelastic testing variables in 21 cats administered enoxaparin or 0.9% NaCl

		Enoxaparin				0.9% NaCl			
Variable	**Timepoint**	**Obs.**	**Mean**	**SD**	***P*-value**	**Obs.**	**Mean**	**SD**	***P*-value**
Clotting time (s)	CT T0	21	477.7	52.0		21	451.6	56.2	
	CT T2h	21	593.4	78.1	<.001	21	448.5	50.3	.29
	CT T4h	21	512.0	63.1	.07	21	436.0	67.9	.53
	CT T8h	19	493.8	54.2	.43	20	439.9	88.6	.85
Clot formation time (s)	CFT T0	21	154.6	39.9		21	155.9	36.3	
	CFT T2h	21	183.1	41.7	.001	21	155.4	28.0	.85
	CFT T4h	21	160.7	39.5	.21	21	148.5	28.0	.38
	CFT T8h	19	147.8	29.0	.68	20	143.1	32.2	.49
Alpha angle (°)	α T0	21	57.3	5.0		21	57.3	4.6	
	α T2h	21	52.4	6.1	.003	21	56.7	3.7	.60
	α T4h	21	55.4	6.7	.32	21	57.6	4.5	.60
	α T8h	19	57.1	6.6	.80	20	58.6	4.9	.51
Maximum clot firmness (mm)	MCF T0	21	37.1	7.00		21	36.0	5.7	
	MCF T2h	21	36.4	6.4	.82	21	36.1	5.5	.59
	MCF T4h	21	38.2	7.2	.65	21	37.4	6.2	.22
	MCF T8h	19	37.8	6.0	.51	20	37.5	5.0	.75

Abbreviations: CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness; Obs., observations; SD, standard deviation; T0, baseline; T2h, 2 hours after injection; T4h, 4 hours after injection; T8h, 8 hours after injection; α, alpha angle.
All *P*-values for subsequent timepoints are compared to baseline.

2.4 | Anti-Xa assay

One hundred sixty-five whole blood samples were collected from cats in 4% Sodium Citrate and spun for 15 min at a speed of 2000-2500 g, at a temperature of 18°C within 1 hour of collection. The plasma was then frozen at −80°C until measurements could be performed. The anti-Xa test variables were programmed onto the analyzer of the UC Davis Veterinary Medical Teaching Hospital by a licensed Clinical Laboratory Scientist with experience using the STA Compact, under the supervision of a Diagnostica Stago Technical Service Specialist, and in accordance with the manufacturer's specifications for the test. Calibration was verified and set using the STA Multi Hep Calibrator and STA Quality LMWH quality control material per manufacturer recommendations. Quality control was then run on each day of cat analysis and verified by laboratory staff using Westgard rules. In accordance with the manufacturer-provided method validation protocol for anti-Xa, intra run precision was performed by running both low and high levels of quality control 10 times each. Mean and SD was then calculated and verified to fit below the maximum recommendation (LMWH 8 SD 0.02 IU/mL < 0.1 Target SD, LMWH 14 SD 0.04 IU/mL < 0.1 Target SD). Intra-lab precision was also conducted across 7 days with 2 runs of quality control per day to obtain a passing total precision that was below the maximum manufacturer limits (LMWH 8 SD of 0.04 < 0.1 Target SD and LMWH 14 SD of 0.08 < 0.1 Target SD).

Ten frozen plasma samples were allowed to thaw at room temperature for 20 min and then run on the STA Compact. This cycle was repeated for 5 days until all samples had been analyzed. Results were automatically transmitted from the analyzer to the Lab Information System for verification. Verified samples were then transmitted automatically to the UC Davis VMACS clinical record where they were sorted for statistical analysis.

2.5 | Statistical analysis

A power size calculation was performed using results from a study evaluating effects of LMWHs on thromboelastographic tracings in cats.[12] The variable R-time was chosen for the power analysis for its good correlation with anti-Xa activity from studies in people.[16] A sample size of 21 cats was necessary to achieve a power of 0.82 with an alpha set at 0.05. A power calculation for Pearson's & Spearman's Correlation was additionally performed for the selected sample size of 21 cats. At a significance level set at 0.05, this sample size will detect a correlation of ≥0.6 with a power of 0.84.

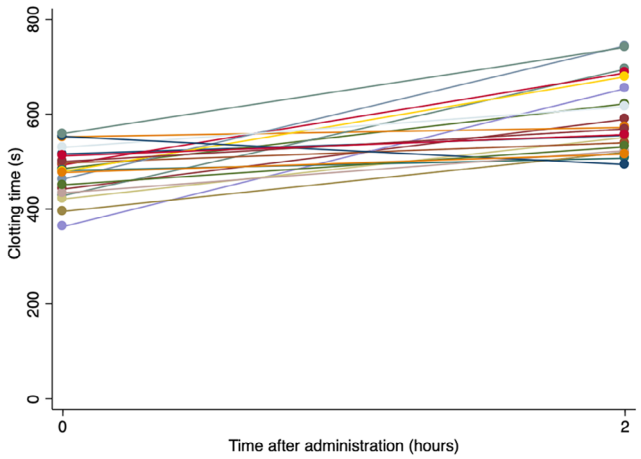

FIGURE 2 Individual changes in clotting time between T0 and T2 in the enoxaparin group

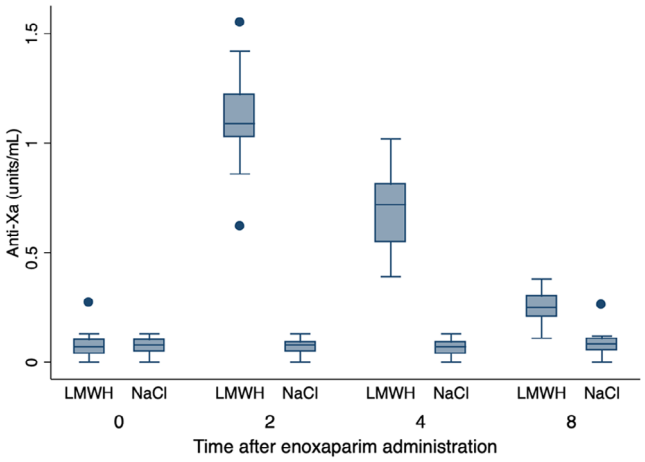

FIGURE 3 Box-and-whisker plots comparing anti-Xa activity between low-molecular-weight heparin (enoxaparin) and 0.9% NaCl groups at T0, T2, T4, and T8. The blue dots represent outliers.

TABLE 2 Anti-Xa Activity in 21 cats administered enoxaparin or 0.9% NaCl

	Enoxaparin				NaCl 0.9%			
Time	Obs.	Mean	SD	*P*-value	Obs.	Mean	SD	*P*-value
T0	21	0.08	0.06		21	0.07	0.04	
T2h	21	1.12	0.22	<.001	21	0.07	0.04	.97
T4h	21	0.70	0.17	<.001	21	0.07	0.04	.91
T8h	19	0.25	0.07	<.001	19	0.08	0.06	.74

Abbreviations: max, maximum; min, minimum; Obs., observations; SD, standard deviation; T0, baseline; T2h, 2 hours after injection; T4h, 4 hours after injection; T8h, 8 hours after injection.
All *P*-values for subsequent timepoints are compared to baseline.

TABLE 3 Comparison of 95% confidence intervals for VCM-Vet clotting time and AntiXa activity between baseline and 2 hours after administration of enoxaparin in 21 cats

		Clotting time (s)		AntiXa Activity	
Timepoint	Obs.	Mean (SE)	95% CI	Mean (SE)	95% CI
T0	21	477.7 (11.4)	454.0-501.4	0.08 (0.01)	0.05-0.10
T2	21	593.4 (17.0)	557.9-629.0	1.12 (0.05)	1.02-1.22

Abbreviations: CI, confidence interval; CT, clotting time; Obs., observations; SE, standard error; T0, baseline; T2, 2 hours after administration.

Descriptive statistics were done. Each variable was tested for normality using a Shapiro-Wilk test. To look for differences between the treated and control cats either a *t*-test or Mann-Whitney test was done. A Generalized Linear Model was completed to assess changes between baseline measurements (treated vs. controls) and all time points for treated and control cats.[23] Each VCM-Vet measurement and the measure for AntiXa was used as the dependent variable; independent variables were created for baseline, for each time point, and for the interaction between the before and after administration times with each cat considered a random variable. To look for correlation between changes in CT values and AntiXa values a Spearman's correlation test was done. Statistical analysis was done using a commercially available software program (Stata/IC version 14.2; StataCorp, College Station, Texas, USA). $P < .05$ was considered significant.

3 | RESULTS

All 21 cats were male neutered. Age was not normally distributed, while weight was. Median age was 3.6 years (interquartile range, 3.6-6.5 years). Mean weight ± SD was 4.31 ± 0.56 kg. No CBC, PCV, TP or blood smear abnormalities were detected. Samples were not obtained at 2 timepoints for 2 cats. One cat did not tolerate handling at that timepoint, and 1 cat developed bruising in the jugular area.

There were no significant differences in any VCM-Vet variables and anti-Xa activity between groups at baseline. Significant differences in the enoxaparin group at 2 hours compared to baseline and controls were found and presented as mean ± SD for CT (enoxaparin, 593.4 ± 78.0 s; control, 448.5 ± 50.3 s, $P < .001$; Figure 1A), CFT (enoxaparin, 183.1 ± 41.7 s; control, 155.4 ± 28.0 s, $P = .001$; Figure 1B) and α-A (enoxaparin, 52.4 ± 6.1°; control, 56.9 ± 3.7°, $P = .003$; Figure 1D), but not for MCF (Figure 1C). These were not significant at the 4- and 8-hour timepoints. All measurements for VCM-Vet testing variables are presented in Table 1. All but 1 cat had an increase in CT value from T0 to T2. These individual changes in CT can be seen in Figure 2.

AntiXa activity was significantly different between T0 and all other timepoints for the enoxaparin group (Table 2, Figure 3), but not for the saline group. All individual cats had an increase in AntiXa activity after administration of enoxaparin at 2 hours after injection. There was no correlation between the change in CT values and the change in antiXa activity at different timepoints ($P = .38$), however the 95% confidence intervals for both CT and antiXa activity did not overlap between the T0 and T2 timepoints respectively (Table 3) indicating that an increase in antiXa activity can be predicted by an increase in CT even if it cannot predict the magnitude of that change.

There were no significant differences in any timepoints for VCM-Vet variables and anti-Xa activity in the control group. MCF was not significantly different in any group at any timepoint.

4 | DISCUSSION

This study found that the effects of a single subcutaneous injection of enoxaparin (1 mg/kg) administered to healthy cats can be detected using the VCM-Vet. There was a significant increase in CT and decrease in α-angle and CFT, 2 hours after administration of enoxaparin. Values returned to baseline at 4 hours and remained as such 8 hours after administration. There were differences in anti-Xa activity in all timepoints. However, there was no correlation between VCM-Vet variables and anti-Xa activity at any timepoint. Such differences were not found in the timepoint matched cross over control group.

Changes in CT interpreted as hypocoagulability were most substantial at T2 through to T4 time points in this study. This timepoint is similar to peak anti-Xa activity from previous studies of LMWH administration in cats.[10,11] Furthermore, current guidelines for anti-Xa activity testing recommend sampling to be performed 3-4 hours after heparin administration.[24] Given that anti-Xa activity testing is not readily available and could be cost-prohibitive, the VCM-Vet device might prove a valuable in-house alternative for monitoring cats receiving heparin.

Our findings suggest that a single therapeutic subcutaneous dose of enoxaparin can induce changes compatible with hypocoagulability in healthy cats. These changes affected 3 of the 4 main VCM-Vet variables, with exception to MCF. Changes in α-A and CFT remained relatively mild (within established reference intervals[20]) and CT was slightly above the proposed reference intervals even at baseline. The relevance of this finding should not be overinterpreted since differences in reference intervals between devices are not uncommon. Indeed, PROVETS viscoelastic coagulation testing guidelines recommending establishment of reference intervals in each center.[25] The increase in CT overtime, while not substantial demonstrates sufficient difference that can be used to make a more informed clinical decision to adjust doses, especially in the absence of alternatives (eg, veterinary anti-Xa activity testing is not available in New Zealand). These findings partially corroborate results in people undergoing orthopedic surgery, where administration of enoxaparin resulted in transient increases in TEG variables (namely r-time).[16] Interestingly, in a small group of healthy cats only administration of UFH led to TEG tracing changes, while administration of enoxaparin (at similar doses as the current study) and deltaparin did not.[12] This could suggest that the

VCM-Vet is more sensitive in detecting anticoagulant-induced hypocoagulability, than TEG. However, a direct comparison of different devices is not recommended by the veterinary guidelines for use of viscoelastic testing.[26]

A recent study comparing VCM-Vet and TEG variables in healthy cats found a strong correlation between CT and TEG variable r-time and a mild positive correlation between MCF and maximum amplitude, respectively, but no other variables were correlated.[20]

This study found changes in anti-Xa activity in the enoxaparin-treated group at all subsequent timepoints after baseline. They exceeded currently recommended therapeutic target of 0.35-0.7 U/mL[7] at T2, were within this target at T4 and fell below the target at T8. This corroborates findings from a small experimental study investigating pharmacokinetics with similar doses of enoxaparin in healthy cats. In this study, anti-Xa activity remained within currently recommended therapeutic target up to 4 hours after enoxaparin administration.[11] This is in contrast with small experimental study investigating effects of enoxaparin in a venous stasis model, which found anti-Xa activity to vary significantly within timepoints.[9] In another small experimental study UFH, but not enoxaparin nor deltaparin reached therapeutic target anti-Xa activity in 4, 8, and 12 hours, respectively.[12] In contrast, 1 small experimental study investigating pharmacokinetics of deltaparin in healthy cats reported dose-related changes in anti-Xa activity, peaking at 2 hours and returning below current therapeutic targets at 8 hours.[10] Since each experiment had a different design, dosages and potentially anti-Xa activity assay, a direct comparison of findings is difficult. However, all these results suggest that there is variation in anticoagulant activity and this needs to be taken into consideration when using this variable for monitoring cats.

This study found no correlation between anti-Xa activity and VCM-Vet variable CT. While some previous studies in people demonstrated a correlation between viscoelastic testing variables and anti-Xa activity, such findings were not consistent.[16,27-29] One small experimental study in healthy dogs demonstrated a strong correlation between TEG variable r-time and anti-Xa activity.[30]

Anti-Xa activity is not commonly used for monitoring people receiving LMWH.[31,32] This is most likely because of the increased safety profile of LMWH, suggesting that monitoring should be reserved for cases at higher risk (pregnant women, people with cancer, obesity, kidney disease).[33] Large clinical trials assessing efficacy of anti-Xa activity monitoring in people are seemingly lacking. Furthermore, the technique does not seem to be standardized, making direct comparison difficult and contributes to the discrepant findings mentioned above.[31-33] Therefore, future studies should perhaps not seek to substitute anti-Xa activity assays with viscoelastic assays, but rather design trials focusing on standardization of viscoelastic assays for monitoring cats, independent of their relationship with anti-Xa activity.

This study has several limitations mostly because of its experimental nature. Conventional coagulation monitoring was not done at any timepoint. However, these healthy research-purposed cats were unlikely to have an underlying coagulopathy. Baseline CT was above established reference intervals in this group, the relevance of which is unknown. Current viscoelastic assay guidelines recommend establishment of in-house reference intervals as they might vary between devices.[25] Finally, the effects of only a single dose of enoxaparin were evaluated, which does not reflect clinical practices where anticoagulants are usually administered over several days.

ACKNOWLEDGMENT

Funding provided by Center for Companion Animal Health at University of California-Davis, USA, and Wenzel Fund for Feline Research at Massey University, New Zealand, RM22764.

CONFLICT OF INTEREST DECLARATION

Entegrion, Inc. provided the VCM-Vet devices and cartridge, but had no influence on the study design, data interpretation or manuscript writing.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the Massey University Animal Ethics Committee (Protocol 19/109).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Ivayla D. Yozova https://orcid.org/0000-0001-6629-0221
Michael S. Kent https://orcid.org/0000-0002-7703-7720
Karl E. Jandrey https://orcid.org/0000-0002-2730-7817

REFERENCES

1. Goggs R, Blais MC, Brainard BM, et al. American College of Veterinary Emergency and Critical Care (ACVECC) Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE) guidelines: small animal. *J Vet Emerg Crit Care (San Antonio)*. 2019;29(1):12-36.
2. Hogan DF. Feline cardiogenic arterial thromboembolism: prevention and therapy. *Vet Clin North Am Small Anim Pract*. 2017;47(5):1065-1082.
3. Goggs R, Bacek L, Bianco D, Koenigshof A, Li RHL. Consensus on the rational use of antithrombotics in veterinary critical care (CURATIVE): domain 2-defining rational therapeutic usage. *J Vet Emerg Crit Care (San Antonio)*. 2019;29(1):49-59.
4. Lo ST, Walker AL, Georges CJ, Li RH, Stern JA. Dual therapy with clopidogrel and rivaroxaban in cats with thromboembolic disease. *J Feline Med Surg*. 2022;24(4):277-283.
5. Smith SA, Tobias AH, Jacob KA, Fine DM, Grumbles PL. Arterial thromboembolism in cats: acute crisis in 127 cases (1992-2001) and long-term management with low-dose aspirin in 24 cases. *J Vet Intern Med*. 2003;17(1):73-83.
6. Borgeat K, Wright J, Garrod O, Payne JR, Fuentes VL. Arterial thromboembolism in 250 cats in general practice: 2004-2012. *J Vet Intern Med*. 2014;28(1):102-108.
7. Sharp CR, de Laforcade AM, Koenigshof AM, Lynch AM, Thomason JM. Consensus on the rational use of antithrombotics in veterinary critical care (CURATIVE): domain 4-refining and monitoring antithrombotic therapies. *J Vet Emerg Crit Care (San Antonio)*. 2019;29(1):75-87.

8. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):188S-203S.
9. Van De Wiele CM, Hogan DF, Green HW 3rd, Sederquist KD. Antithrombotic effect of enoxaparin in clinically healthy cats: a venous stasis model. *J Vet Intern Med*. 2010;24(1):185-191.
10. Mischke R, Schmitt J, Wolken S, Bohm C, Wolf P, Kietzmann M. Pharmacokinetics of the low molecular weight heparin dalteparin in cats. *Vet J*. 2012;192(3):299-303.
11. Mischke R, Schonig J, Doderlein E, Wolken S, Bohm C, Kietzmann M. Enoxaparin: pharmacokinetics and treatment schedule for cats. *Vet J*. 2014;200(3):375-381.
12. Alwood AJ, Downend AB, Brooks MB, et al. Anticoagulant effects of low-molecular-weight heparins in healthy cats. *J Vet Intern Med*. 2007;21(3):378-387.
13. Coppell JA, Thalheimer U, Zambruni A, et al. The effects of unfractionated heparin, low molecular weight heparin and danaparoid on the thromboelastogram (TEG): an in-vitro comparison of standard and heparinase-modified TEGs with conventional coagulation assays. *Blood Coagul Fibrinolysis*. 2006;17(2):97-104.
14. Gerotziafas GT, Chakroun T, Samama MM, Elalamy I. In vitro comparison of the effect of fondaparinux and enoxaparin on whole blood tissue factor-triggered thromboelastography profile. *Thromb Haemost*. 2004;92(6):1296-1302.
15. Zmuda K, Neofotistos D, Ts'ao CH. Effects of unfractionated heparin, low-molecular-weight heparin, and heparinoid on thromboelastographic assay of blood coagulation. *Am J Clin Pathol*. 2000;113(5):725-731.
16. Tekkesin N, Tekkesin M, Kaso G. Thromboelastography for the monitoring of the antithrombotic effect of low-molecular-weight heparin after major orthopedic surgery. *Anatol J Cardiol*. 2015;15(11):932-937.
17. Burton AG, Jandrey KE. Use of thromboelastography in clinical practice. *Vet Clin North Am Small Anim Pract*. 2020;50(6):1397-1409.
18. Buriko Y, Drobatz K, Silverstein DC. Establishment of normal reference intervals in dogs using a viscoelastic point-of-care coagulation monitor and its comparison with thromboelastography. *Vet Clin Pathol*. 2020;49(4):567-573.
19. Rigor RR, Schutzman LM, Galante JM, Brown IE. Viscoelastic coagulation monitor (VCMVet) reference intervals and sex differences in mature adult mice. *Acta Haematol*. 2021;144(6):633-640.
20. Rosati T, Jandrey KE, Burges JW, Kent MS. Establishment of a reference interval for a novel viscoelastic coagulometer and comparison with thromboelastography in healthy cats. *Vet Clin Pathol*. 2020;49(4):660-664.
21. Loughran KA, Rush JE, Rozanski EA, Oyama MA, Larouche-Lebel E, Kraus MS. The use of focused cardiac ultrasound to screen for occult heart disease in asymptomatic cats. *J Vet Intern Med*. 2019;33(5):1892-1901.
22. Flatland B, Koenigshof AM, Rozanski EA, Goggs R, Wiinberg B. Systematic evaluation of evidence on veterinary viscoelastic testing part 2: sample acquisition and handling. *J Vet Emerg Crit Care (San Antonio)*. 2014;24(1):30-36.
23. Gardiner JC, Luo Z, Roman LA. Fixed effects, random effects and GEE: what are the differences? *Stat Med*. 2009;28(2):221-239.
24. Center CUAHD. Anticoagulant monitoring news and notes. https://www.vet.cornell.edu/animal-health-diagnostic-center/news/anticoagulant-monitoring-news-and-notes#:~:text=Collect%20blood%20samples%20at%203,Assay%20method%20%3D%20anti%2DXa%20activity. 2022.
25. Hanel RM, Chan DL, Conner B, et al. Systematic evaluation of evidence on veterinary viscoelastic testing part 4: definitions and data reporting. *J Vet Emerg Crit Care (San Antonio)*. 2014;24(1):47-56.
26. McMichael M, Goggs R, Smith S, Wagg C, Warman S, Wiinberg B. Systematic evaluation of evidence on veterinary viscoelastic testing part 1: system comparability. *J Vet Emerg Crit Care (San Antonio)*. 2014;24(1):23-29.
27. Bhatia AK, Yabrodi M, Carroll M, et al. Utility and correlation of known anticoagulation variables in the management of pediatric ventricular assist devices. *World J Cardiol*. 2017;9(9):749-756.
28. Dias JD, Lopez-Espina CG, Panigada M, Dalton HJ, Hartmann J, Achneck HE. Cartridge-based thromboelastography can be used to monitor and quantify the activity of unfractionated and low-molecular-weight heparins. *TH Open*. 2019;3(3):e295-e305.
29. Magunia H, Schenk S, Schlensak C, et al. Detection of early incomplete heparin reversal following congenital cardiac surgery: a single-center retrospective observational study. *Thromb Res*. 2019;182:33-38.
30. McLaughlin CM, Marks SL, Dorman DC, Motsinger-Reif A, Hanel RM. Thromboelastographic monitoring of the effect of unfractionated heparin in healthy dogs. *J Vet Emerg Crit Care (San Antonio)*. 2017;27(1):71-81.
31. Hutt Centeno E, Militello M, Gomes MP. Anti-Xa assays: what is their role today in antithrombotic therapy? *Cleve Clin J Med*. 2019;86(6):417-425.
32. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e24S-e43S.
33. Lin A, Vazquez SR, Jones AE, Witt DM. Description of anti-Xa monitoring practices during low molecular weight heparin use. *J Thromb Thrombolysis*. 2019;48(4):623-628.

How to cite this article: Yozova ID, Kent MS, Jandrey KE. Effects of a single subcutaneous dose of enoxaparin on veterinary viscoelastic coagulation monitor variables in healthy cats: Double blind, placebo controlled cross-over trial. *J Vet Intern Med*. 2023;37(1):133-139. doi:10.1111/jvim.16602