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D-dimer Analysis in Dogs With Hypercoagulable Diseases

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Abstract : Total 283 dogs were enrolled in this study (control group: 140, patient group: 143). In the patient group, 143 dogs with underlying diseases including immune medicated hemolytic anemia (IMHA) (7), lymphoma (30), hyperadrenocorticism (HAC) (16), trauma (10), pyometra (8), bone fracture (38), peritonitis (13), meningoencephalitis (12) and mitral regurgitation (9) were enrolled in this study. Compared with healthy group, lymphoma, trauma, HAC, and IMHA group showed significantly ($P < 0.01$) high values of D-dimer and the highest levels in the IMHA group. Additionally, we evaluated the D-dimer level after a week of enoxaparin treatment, and the results showed D-dimer levels of post treatment group were significantly decreased compared to the pre-treatment group in lymphoma, HAC, trauma and IMHA diseases. In the high level D-dimer group, post D-dimer values after enoxaparin treatment had significantly decreased ($P < 0.01$) compared to levels prior to treatment.

Key words **:** D-dimer, dog, enoxaparin, levels, underlying diseases.

Introduction

D-dimer is a specific fibrin degradation product that yields plasmin-mediated lysis of cross-linked fibrin (1). D-dimer indicates both thrombin and plasmin generation and is specific for fibrinolysis (3). Elevated D-dimer concentrations have been reported in dogs with DIC, hemorrhage, neoplasia, renal disease, thromboembolic disease, liver disease, and post-surgery (2).

Therefore, it is an ancillary diagnostic tool for disseminated intravascular coagulation (DIC) and an indirect marker of hypercoagulability (7). As a marker of hypercoagulability, the sensitivity and the specificity of D-dimer for detection of hypercoagulable states in animals with various disease such as neoplasia or heart disease is unknown (1). A D-dimer assay should not be the sole test for the purpose of the detection of a hypercoagulable state, but could be used together with other markers of thrombin generation such as thromnin-antithrombin complex (1).

Hypercoagulable states include many acquired disorders which have an increased risk for thromboembolism (11). In veterinary medicine, thrombosis is considered a cause of death in some hypercoagulabe diseases such as immune medicated hemolytic anemia (IMHA) and hyperadrenocorticism (HAC). This study was performed to evaluate the D-dimer levels and anti-thrombin medication effect in the hypercoagulabe diseases.

Materials and Methods

Animals

Total 283 dogs were enrolled in this study. For the control group, the owners of the 140 dogs had previously shown interest in this clinical study were determined to be healthy based on the results of a physical examination, complete blood count, serum biochemistry, electrolyte analysis and radiologic examination including X-ray and ultrasonography. In the patient group, 143 dogs with underlying diseases including IMHA (7), lymphoma (30), HAC (16), trauma (10), pyometra (8), bone fracture (humerus: 15, femur: 23), peritonitis (13), meningoencephalitis (ME; 12) and mitral regurgitation (MR; 9) were present in the study.

Dogs were excluded if they had received medicine such as aspirin, clopidogrel, heparin and enoxaparin that could have altered D-dimer results at the time of presentation and clinical suspicion whether they had a concurrent disease other than above mentioned diseases. Lymphoma was diagnosed by histopathologic examination. HAC was diagnosed based on positive: a low-dose dexamethasone suppression test or ACTH stimulation test with enlarged adrenal gland on abdominal ultrasonography.

Sampling

Blood was collected from all dogs using jugular venipuncture with 23-G needle. Blood was collected directly into sample tubes: 1 ml EDTA tube for complete cell count analysis, and 0.5 ml 3.2% sodium citrate tubes for a final blood to citrate ratio of 9: 1 for D-dimer analyses. Serum biochemistry and complete cell count analysis was run within 5 minutes of sample collection.

D-dimer analysis

Plasma D-dimer was measured using D-dimer [Nycocard, Alere, USA]. In case of high value D-dimer patients, enoxaparin [CLEXANE, Sanofi-Winthrop Lodustrie, France, 1 mg/kg SC, BID] was administered and post treatment D-dimer value was measured.

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Statistical analysis

Statistical analysis was performed using SPSS Statistics 20.0.0 (SPSS Inc., USA). A P value of < 0.05 was considered significant. An paired *t*-test for D-dimer analysis was used to compare normally distributed data and Wilcoxon signed rank test was used for nonparametric data.

Results

In the control group, D-dimer values were 0.19 ± 0.08 μg/dL (Mean ± SD) (Table 1). D-dimer values of lymphoma, trauma, HAC, pyometra and IMHA groups were 2.29 ± 0.97 μg/dL (Mean ± SD), 3.89 ± 2.49 μg/dL (Mean ± SD), 3.28 ± 2.56 μg/dL (Mean ± SD), 1.42 ± 2.12 μg/dL (Mean ± SD) and 5.49 ± 2.57 μg/dL (Mean ± SD) respectively (Table 1). In the patient group, D-dimer values of ME, MR (ACVIM stage C), peritonitis, and bone fracture groups were 0.3 ± 0.29 μg/dL (Mean ± SD), 0.4 ± 0.64 μg/dL (Mean ± SD), 0.33 ± 0.37 μg/dL (Mean ± SD), and 0.23 ± 0.12 μg/dL (Mean ± SD) respectively (Table 1). Compared with the healthy group, lymphoma, trauma, HAC, and IMHA groups showed significantly ($P < 0.01$) high values of D-dimer (Table 1). Post D-dimer levels after enoxaparin treatment were significantly decreased ($P < 0.01$) compared to pre-treatment in the lymphoma, trauma, HAC, and IMHA groups.

Table 1. D-dimer value of enrolled control and patient groups

Group	Disease	D-dimer value (μg/dL)	Medication	Post D-dimer value (μg/dL)
Control group	Healthy n = 140	0.19 ± 0.08	N	N
Patient group	Lymphoma N = 30	2.29 ± 0.97*	Enoxaparin	0.32 ± 0.14**
	Trauma n = 10	3.89 ± 2.49*	Enoxaparin	0.22 ± 0.12**
	ME n = 12	0.3 ± 0.29	Enoxaparin	0.16 ± 0.05
	HAC n = 16	3.28 ± 2.56*	Enoxaparin	0.26 ± 0.1**
	Pyometra n = 8	1.42 ± 2.12	Enoxaparin	0.35 ± 0.07
	MR n = 9	0.41 ± 0.64	N	N
	IMHA n = 7	5.48 ± 2.56*	Enoxaparin	0.31 ± 0.14**
	Peritonitis n = 13	0.33 ± 0.37	N	N
	Bone fracture n = 38	0.22 ± 0.12	N	N

n = enrolled patient number, N = none
All D-dimer values were described mean ± SD (standard deviation)
*$P < 0.01$ significant difference between control and patient groups
**$P < 0.01$ significant difference between pre and post treatment D-dimer value
HAC: hyperadrenocorticism; IMHA: immune medicated hemolytic anemia; MR: mitral regurgitation
ME: meningoencephalitis

Discussion

Thrombosis is a consequence of a hypercoagulable state such as IMHA, HAC, and neoplasia, blood stasis including left atrium enlargement, and damage to the endothelium of blood vessels (11). In veterinary patients, PTE is often associated with other common underlying diseases and conditions (3). This fact often makes diagnosis of PTE difficult because common signs often include tachypnea and dyspnea, which are also prevalent in other cardiopulmonary diseases (5). Predisposing diseases associated with PTE include heartworm disease, IMHA, HAC, pancreatitis, diabetes mellitus, protein losing nephropathy, nephritic syndrome, sepsis, systemic inflammatory response syndrome (SIRS), cardiomyopathy, neoplasia, and trauma (4,8).

In this study, we surveyed the D-dimer value among the hypercoagulable diseases. From the current study, we found that lymphoma, HAC, trauma and IMHA patient had significantly high levels of D-dimer compared with that of healthy control individuals. D-dimer is a degradation byproduct of cross-linked fibrin and increased D-dimer levels have been documented in dogs with DIC, neoplasia, thrombolic disease (2). Few studies have been reported the usefulness of D-dimer levels in veterinary patients (2,7). According to Nelson *et al*. (7), the sensitivity of D-dimer concentrations above 5.0 ng/mL for predicting TE was 100% and FDPs were not high in any TE patient. Other laboratory markers of coagulation activation have been proposed and used for TE diagnosis in people; however, only the D-dimer assay has shown clinical utility in veterinary medicine (2).

Enoxaparin is a low molecular weight heparin (LMWH) and used for IMHA patients for the prevention of thromboembolism in veterinary medicine (6,9,10). From this study, we cannot guarantee that only high-level D-dimer values represent a hypercoagulable state or high-risk of thromboembolism. However, we found that D-dimer values levels were high in well-known hypercoagulable disease such as lymphoma, HAC, trauma, IMHA. D-dimer levels significantly decreased after enoxaparin treatment as an anti-thrombin medicine.

The result may suggest that D-dimer assay is needed to predict the possibility of development to thromboembolsim in hypercoagulable diseases such as lymphoma, HAC, trauma, and IMHA patients.

And also, this study suggests that anti-thrombin medication is needed to decrease the possibility of thromboembolic disease.

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