Evaluation of von Willebrand factor in dogs with parvoviral enteritis

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ABSTRACT

Canine parvoviral enteritis may lead to coagulopathy in various ways. In recent years, the importance of the von Willebrand factor has become the focus of more attention in infectious diseases. This study aimed to determine the significance of von Willebrand factor level and coagulation parameters in dogs with parvoviral enteritis. The experimental group of this study consisted of 20 dogs with parvoviral enteritis of different breeds aged 2-6 months, and the control group consisted of 10 healthy dogs aged 2-6 months. Blood samples were taken from the dogs included in the experimental group at the 0th hour, 24th hour and before discharge, and only at the 0th hour from the healthy puppies in the control group The 0th and 24th hour von Willebrand factor values of the trial were significantly higher than the control group. The 0th hour Prothrombin Time of the trial was significantly prolonged compared to the control group. The 0th hour Activated Partial Thromboplastin Time value of the trial was significantly prolonged compared to the before-discharge and control group. The before-discharge fibrinogen level was considerably lower than at 0th and 24th hours of the trial. In conclusion, von Willebrand factor concentrations, which increase significantly in dogs with parvoviral enteritis compared to healthy animals, can be evaluated as an acute phase protein. Prolongation of Prothrombin Time and Activated Partial Thromboplastin Time and no significant change in fibrinogen and D-dimer values demonstrated that dogs with parvoviral enteritis were in the hypercoagulation state without disseminated intravascular coagulation.

Introduction

Canine Parvovirus infection (CPV) is caused by two types of parvovirus; canine parvovirus type-1 (CPV-1) and canine parvovirus type-2 (CPV-2). CPV-1 or known as canine minute virus, are genetically and antigenically completely different from CPV-2. CPV-1 has low pathogenicity in dogs and can cause gastroenteritis, pneumonia or myocarditis, in puppies 1-3 weeks old. CPV-2 (or killer virus, infectious enteritis virus, intestinal flu virus or puppy heart virus) causes vomiting and bloody diarrhoea in puppies aged six weeks to 6 months. (1, 2, 7, 8, 15, 19, 26).

Clinical parvovirus infections have two clinical manifestations. These are the acute forms of hemorrhagic enteritis and myocarditis. Fetal contamination plays an important role in myocarditis form. Sudden death may occur in newborns infected with CPV shortly after birth as a result of interstitial myocarditis and congestive heart failure. Because the cardiac muscle cells of neonatal animals have high mitotic activity, and the virus directly infects the cardiac muscle cells (4, 5, 21).

The most characteristic clinical form of canine parvoviral enteritis is reported as hemorrhagic enteritis (8, 9, 11, 20, 22, 24). When Parvoviruses infect the germinal epithelium of intestinal crypts, they cause epithelial destruction and villous collapse. Bloody diarrhoea occurs in the small intestine as a result of impaired cell destruction leading to the characteristic pathological lesions that are shortened and atrophic. Clinical signs of the disease usually appear after an incubation period of 3-7 days. In cases with hemorrhagic enteritis, clinical signs are anorexia, depression, vomiting, mucoid or bloody diarrhoea, dehydration, and fever (1, 8, 9,20).

Von Willebrand factor (vWF) plays a crucial role in coagulation, platelet adhesion, and thrombus formation. vWF is a high molecular weight multimeric glycoprotein. This factor is a protein that provides the adhesion of platelets to the sub-endothelial tissue and thrombus formation. It also acts as a carrier for factor VIII. In addition, it has been found to increase in inflammation by acting as an acute phase protein in recent years. (6, 12).

One of its two most important roles in hemostasis is to help the adhesion and aggregation of platelets on the damaged vessel wall and the other is to transport factor VIII to the damaged area. vWF is required for platelet adhesion to the capillary vessel wall and subsequent aggregation. Therefore, in the VWF deficiency, bleeding occurs in the capillary-rich mucosal surface and skin (14, 17).

The present study was designed with the hypothesis that CPV may lead to changes in vWF concentrations in infected dogs. This study evaluated vWF factor, a disintegrin and metalloprotease with thrombospondin type motifs-13 (ADAMTS-13) and coagulation parameters in dogs with parvoviral enteritis.

Materials and Methods

Animal Material: This study consisted of 20 dogs with parvoviral enteritis (experimental group) and ten healthy dogs (control group) aged between 8-22 weeks admitted to the Department of Internal Medicine, Faculty of Veterinary Medicine, Selcuk University. Ethical approval (2017/011) was obtained from the Selcuk University Faculty of Veterinary Medicine Ethics Committee (SÜVFEK).

Clinical Examination: Anamnesis, physical and laboratory examination findings were recorded in dogs admitted to the animal hospital with complaints of vomiting, anorexia and bloody diarrhoea. The faecal rapid antigen test (Asan Easy Test PARVO, Asan Pharma, CO. LTD. Gyonggi-do Korea) was applied to the animals suspected of parvoviral infection. Dogs with positive test results were included in the study. During the routine clinical examinations of the dogs with parvoviral enteritis; body temperature, heart and respiratory rates, mucous membrane colour, peripheral pulse quality, hydration and mental status were recorded. Routine clinical and laboratory (hemogram, blood gases and serum biochemistry) examinations and faeces test were applied to dogs. Dogs with normal clinical, laboratory findings and negative faeces parvovirus antigen test were considered healthy and were included in the control group.

Collection, storage and analysis of blood samples: Blood samples were taken from the anterior leg vena cephalica antebrachii, with anticoagulant (K3-EDTA), sodium-citrate and heparin) and without anticoagulant, before treatment (0^{th} hour), 24^{th} hours after treatment and before discharge. Hemogram and blood gas analyses were immediately performed. Melet Schloesing MS4-e Hematology Analyzer (France) was used for hemogram analysis. ABL 90 flx Radiometer (radiometer medical ApS Aakandevej 21, DK-2700 Bronshoji, Denmark) was used for blood gas analysis.

Measurement of vWF and coagulation profile: Blood samples were centrifuged at 5000 rpm for 5 minutes. Plasma samples were stored at -20°C freezer until the measurement for vWF, activated partial thromboplastin time (APTT), prothrombin time (PT), D-Dimer and fibrinogen. Intra-assay (within-assay) and inter-assay (inter-assay) coefficient of variation (CV) reported for von Willebrand factor <8% and <12%, respectively, detection range 0.15-70 ng Intra-assay and inter-assay coefficient of variation reported for /mL (vWF, (Catalog # MBS286695, Lot # L06RVW25, My BioSource, USA). Canine specific vWF was measured in ELISA devices with commercial test kits. Coagulation profiles were PT (catalogue no: OUHP-49, Siemens Innovin Germany), APTT (catalogue no: OQGS-29 Actin Germany), D-dimer (catalogue no: OPBP-03, Innovance) d-dimer Germany) and fibrinogen (catalogue no: OWZG-15, Multifibrin U Germany) levels were also measured in a Sysmex CA 150 device (Siemens) in a private laboratory.

Treatment Protocol: Dogs with parvoviral enteritis were taken to the infection or intensive care unit according to the severity of the disease and hospitalised for 5-8 days. Treatment was initiated following the detection of parvovirus in the test results.. For those with low blood pH, 0.9% NaCl (Poliflex 0.9% isotonic sodium chloride, Polifarma) 20 mL/kg intravenously, Ringer's lactate (Poliflex lactated Ringer's, Polifarma) 65 mL/kg/ and 5% dextrose (Poliflex 5% dextrose, Polifarma) 5mL/kg intravenously was applied as a standard. The patients were given b complex and amino acid solutions (Duphalyte, Zoetis) and vitamin C (Vita C Vetoquinol) as supportive treatment. In addition, Metoclopramide (Metpamid, Recordanti) at a dose of 0.03 mg/kg intravenously every 8 hours or as a continuous infusion at a dose of 0.1-0.2 mg/kg/day intravenously and Ranitidine (Ranixel, Menta Pharma) 1-5 mg/kg intravenously given every 8 hours were given to patients. Cefazolin (Iespor®, İbrahim Ethem, Ulagay or Equizolin®, Tüm-Ekip İlaç AŞ) 22 mg/kg intravenously, TID and Enrofloxacin (Baytril® Bayer) 5 mg/kg intravenously, SID, combination was administered to patients with fluid therapy. The recovered dogs were discharged from the hospital.

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Statistical Analysis: SPSS 25 (IBM Corp®, 2017, Armonk, NY, USA) statistical program was used to evaluate the data. The Kolmogorov–Smirnov test determined the variables' normality and the variances' homogeneity. Since the variables do not have a normal distribution, the study data are presented as median (min/max) and were evaluated using the Friedman test. Statistical significance was considered as $P<0.05$.

Results

Clinical Examination Findings: At the first clinical examination, all patients had complaints of anorexia and stagnation. During the first clinical examination of the patients, vomiting in 15 cases and hemorrhagic diarrhoea in 8 cases were detected. However, hemorrhagic diarrhoea and vomiting were observed in all patients after 1-2 days. Fever (>39.2°C) was detected in only 9 cases during the initial examination. At the initial examination, the degree of dehydration was >6% in 15 of the 20 dogs. Twenty four hours after first examination, the number of cases of hemorrhagic diarrhea increased to 17, the number of cases with vomiting increased to 19, and the number of cases with high body temperature increased to 10. While the body temperature of only one patient was low during the first examination, this number increased to 3 after 24 hours. Despite treatment, one patient died within the first 24 hours. Forty eight hours after examination, all cases had hemorrhagic diarrhoea and vomiting. During this time, a dog died. Vomiting disappeared in all 18 surviving dogs before discharge, and body temperature, appetite and stool returned to normal.

Hemogram and Blood Gases Findings: Although granulocyte values were significantly lower in the experimental group than in the control group at the 0^{th} and 24^{th} hours, they increased until discharge and were insignificantly lower than the control group. The erythrocyte values of the experimental group at the 0^{th} and 24^{th} hours were insignificant compared to the control group. However, the 0^{th} hour erythrocyte values of the experimental group were significantly higher than the before discharge values. The hematocrit values in the experimental group at the 0^{th} hour were significantly higher than those in the control group and before discharge. Before discharge hematocrit values were significantly lower than the 0^{th} and 24^{th} hours of the experimental group. Hemoglobin values of the experimental group at the 0^{th} and 24^{th} hours were significantly higher than those in the before discharge and control groups (Table 1).

Table 1. Hemogram values in dogs with parvoviral enteritis and healthy.

Parameter	Control Group	Experimental Group		
		0^{th} hour	**24^{th} hour**	**Before Discharge**
WBC ($x10^3$ /mm^3)	12.88 (6.93/21.75)	10.13 (2.28/9.04)	8.72 (1.12/22.30)	13.15 (4.16/38.54)
Lym ($x10^3$ /mm^3)	4.19 (2.50/8.80)	4.13 (1.27/15.65)	3.20 (0.97/12.98)	4.94 (0.87/22.5)
Mon ($x10^3$ /mm^3)	0.58 (0.25/1.48)	0.41 (0.04/4.35)	0.42 (0.03/5.44)	1.64 (0.15/7.39)
Gran ($x10^3$ /mm^3) ($P<0.02$)	**8.15 (2.19/12.08)^a**	**3.24 (0.21/18.77)^b**	**3.33 (0.12/9.05)^b**	**4.49 (1.87/11.18)^{ab}**
MCV (fl)	59.96 (53.3/65.4)	61.81 (55.9/68.2)	61.09 (53.6/67.8)	58.47 (52.8/64.9)
RBC ($x10^6$ /mm^3) ($P<0.03$)	**6.58 (5.61/8.22)^{ab}**	**7.32 (5.43/10.05)^a**	**6.77 (4.7/9.2)^{ab}**	**5.81 (3.85/7.6)^b**
HCT (%) ($P<0.01$)	**38.23 (33.1/46.1)^{bc}**	**45.03 (3.5/58.4)^a**	**41.18 (27.2/52.7)^{ab}**	**33.78 (23.9/43.3)^c**
MCHC(g/dl)	30.20 (28.7/31.8)	29.85 (28.10/58.90)	30.50 (27.9/49)	32.20 (21.10/37.80)
RDW	11.46 (9.6/13.8)	12.67 (9.4/23.6)	12.68 (9.4/23.6)	13.58 (9.7/24.9)
Hb (g/dl) ($P<0.05$)	**11.62 (9.5/13.9)^{ab}**	**13.42 (9.1/22.7)^a**	**13.50 (8.3/25.2)^a**	**10.82 (7.9/13.4)^b**
THR ($x10^3$ /mm^3)	313.30 (136/514)	425.10 (103/898)	348.21 (40/880)	281.94 (47/598)

The blood pH value at the 0th hour was found to be significantly lower than before discharge. Before discharge, the potassium (K^+) value was significantly lower than the control group. The sodium (Na^+) value at the 0th hour was found to be statistically significantly lower than before discharge. The before discharge calcium (Ca^{++}) concentration was also significantly lower than the 0th and 24th hours and the control group. Blood glucose concentration at the 0th hour was statistically significantly higher than the before discharge values (Table 2).

vWF and Coagulation profile Findings: The experimental group's 0th and 24th hour vWF values were significantly higher than the control group. While experimental group's 0th hour PT and APTT values were significantly higher than the control group, the APTT value at the 24th hour of the experiment remained significantly higher than the control group. However, the PT before discharge value showed insignificant changes compared to the control group (Table 3.4). The fibrinogen concentrations before discharge were significantly lower than in the 0th and 24th hour, and the control group (Table 3).

Table 2. Blood gas values in dogs with parvoviral enteritis and healthy.

Parameter	Control Group	Experimental Group		
		0th hour	**24th hour**	**Before Discharge**
Ph (P<0.04)	**7.38 (7.34/7.41)^{ab}**	**7.34 (7.12/7.46)^{b}**	**7.38 (7.28/7.44)^{ab}**	**7.43 (7.38/7.48)^{a}**
K (mmol/L) (P<0.04)	**3.83 (2.8/4.5)^{a}**	**3.52 (2.6/4)^{ab}**	**3.57 (2.7/4.4)^{ab}**	**3.22 (2.2/4.3)^{b}**
Na (mmol/L) (P<0.03)	**149.80 (145/167)^{ab}**	**145.33 (139/157)^{b}**	**148.17 (139/165)^{ab}**	**153.92 (145/172)^{a}**
Ca (mmol/L) (P<0.04)	**1.19 (0.63/1.45)^{a}**	**1.02 (0.46/1.26)^{a}**	**1.00 (0.65/1.35)^{a}**	**0.77 (0.54/1.1)^{b}**
Cl (mmol/L)	110.80 (107/117)	106.44 (94/115)	107.52 (99/115)	111.14 (102/122)
Laktat (mmol/L)	1.38 (0.7/2)	1.83 (0.5/4.4)	1.68 (0.7/2.7)	1.30 (0.4/3)
BE (mmol/L)	-2.02 (-5.1/2.3)	-2.96 (-13/9.7)	-0.54 (-8/6.6)	-0.42 (-6.4/5.1)
Hco3 (mmol/L)	22.24 (19.6/25.5)	21.37 (13.8/31.6)	23.27 (18.2/29.2)	23.62 (19.1/27.7)

Table 3. Von Willebrand and coagulation parameters values in dogs with parvoviral enteritis and health.

Parameter	Control Group	Experimental Group		
		0th hour	**24th hour**	**Before Discharge**
vWF (ng/ml) (P<0.01)	**2.30 (0.1/5.04)^{b}**	**6.19 (0.1/13.96)^{a}**	**5.29 (0.1/16.23)^{a}**	**4.91 (2.12/9.05)^{ab}**
PT (sn) (P<0.01)	**9.43 (8/12.3)^{b}**	**13.68 (9.2/21.4)^{a}**	**12.62 (8/24)^{ab}**	**10.44 (8/12.60)^{ab}**
APTT (sn) (P<0.02)	**17.15 (14.90/37.10)^{a}**	**32 (22.50/40.30)^{b}**	**28.70 (15.80/105.40)^{bc}**	**17 (14.90/31.20)^{ac}**
D-DİMER (mg/dl)	1.20 (0.51/2.46)	1.18 (0.19/2.31)	0.92 (0.13/1.83)	1.38 (0.51/2.13)
FIBRINOJEN (mg/dl) (P<0.05)	**430.29 (120/684)^{ab}**	**518.14 (334/684)^{b}**	**492.08 (312/684)^{b}**	**276.43 (179/359)^{a}**

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Discussion and Conclusion

In canine parvoviral infections, leukopenia due to neutropenia (granulocytopenia) and lymphopenia is a prominent haematological abnormality. Some researchers (9, 23, 27) reported that 85% of dogs with parvoviral enteritis developed leukopenia due to granulocytopenia (neutropenia) within 72th hours. The granulocytopenia in our study was consistent with their findings (3, 9, 24).

In the presented study, erythrocyte (RBC) and haemoglobin (Hb) concentrations at the 0th and 24th hours were higher than the control group, although not statistically significant. Whereas a significant hyperviscosity is observed due to impaired perfusion as a result of polycythemia in hemorrhagic gastroenteritis (HGE) syndromes, severe anaemia and polycythemia are rarely observed in hemorrhagic diarrhoea due to parvoviral enteritis (30) in various studies on parvoviral enteritis (1, 3, 8, 13). RBC and Hb concentrations were in average reference values, although they were found to be higher than the control group. In the presented study, high RBC and Hb concentrations were consistent with the above mentioned investigators and may be related to splenic contraction and dehydration.

In dogs with parvoviral enteritis, changes in blood gases and serum biochemistry are usually nonspecific (8, 20). In the present study, the blood pH at the 0th hour in dogs with parvoviral enteritis was lower than in the control group, although not statistically significant. However, the pH value at the 0th hour was found to be statistically significantly lower than the values before discharge. Blood K^+, Na^+ and ionised Ca^{++} concentrations were also lower than the control group at 0th hours, although not statistically significant. However, Na^+ and Ca^{++} values at the 0th hour were statistically significantly higher and lower than before discharge. In other words, the animals were evaluated to have metabolic acidosis at admission. The fact that metabolic acidosis was observed in patients at the 0th hour is due to H^+ retention and HCO_3 loss due to diarrhoea. The significant decrease in the K^+ value in dogs with parvoviral enteritis compared to control group is due to the loss of potassium due to vomiting. The decline in Ca++ concentration before discharge may be related transforming free calcium into protein-bound calcium by binding due to increased blood pH (7.43). Our study's nonspecific blood gas results are also consistent with the results of other researchers (1, 8, 13, 20).

Hypercoagulopathy without dissemined intravascular coagulopathy (DIC) has been demonstrated in dogs with canine parvoviral enteritis. Increased vWF levels associated with inflammation and endothelial damage are observed in glomerulonephritis, infectious diseases, arteritis, and sepsis. VWF levels are increased during an acute response of the endothelium. VWF is acute phase reactant indicating endothelial dysfunction and inflammation (28). This suggests that vWF acts like an acute phase protein (6, 10, 18). Acute phase proteins are a non-specific tissue reaction secreted as the body's acute response to inflammation (25). Many researchers (3, 16, 17) reported that acute phase proteins are increased in dogs with parvoviral enteritis and may be a prognostic factor evaluating clinical improvement.. Previous studies (8) found prolongation in PT and APTT and a significant increase in fibrinogen and D-dimer levels in dogs with parvoviral enteritis. They reported that this may indicate of DIC in dogs with parvoviral enteritis. Likewise, another study (13) determined prolongation of PT and APTT, a decrease in fibrinogen level and increase in D-dimer levels in parvoviral enteritis and sepsis. In the present study, vWF levels at the 0th and 24th hours showed a significant increase in dogs with parvoviral enteritis compared to the control group. At the same time, their before discharge values decreased and did not show a significant change compared to the control group. Likewise, our study observed a significant prolongation in PT and APTT at the 0th hour. On the other hand, the D-dimer level did not change statistically. This may be related to the development of hypercoagulopathy without the occurrence of DIC (9, 24). In dogs with parvoviral infection, high concentrations of vWF at the 0th hour and 24th hours act as an acute phase protein, as shown by other authors (6, 10, 18) and it can be considered as the body's acute response to inflammation (25).

In conclusion, vWF concentrations, which increase significantly in dogs with parvoviral enteritis compared to healthy animals, can be evaluated as an acute phase protein. Prolongation of PT and APTT and no significant change in fibrinogen and D-dimer values demonstrated that dogs with parvoviral enteritis were in the hypercoagulation state without DIC.

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Ethical Statement

This study was carried out after the animal experiment was approved by Selcuk University Faculty of Veterinary Medicine Ethics Committee (SÜVFEK) (Decision number: 2017/011).

Conflict of Interest

The authors declared that there is no conflict of interest.

Author Contributions

E.K., and M.S. contributed to conception and design of the study. E.K., M.S. performed the experiments. M.S. and E.K. organized the database. M.S., E.K. performed the statistical analysis. M.S. and E.K. wrote the first draft of the manuscript. E.K. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

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