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The Alterations of Erythrocyte Osmotic Fragility and Hematological Parameters in Puppies with Parvoviral Enteritis in Kirikkale, Türkiye

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Abstract

Canine parvoviral enteritis (CPVe) is an important infectious disease that has pretty high morbidity and mortality rates in puppies, which leads to vomiting and diarrhea range from mucoid to hemorrhagic. The objective of this study to investigate the changes in erythrocyte osmotic fragility (EOF) and hematological parameters in dogs with CPVe. Sixteen healthy and twenty-seven infected male and female dogs identified by the CPV antigen rapid-test kit at ages 2-6 months old were used to collect blood samples. A complete blood count and EOF were measured from the samples. Findings of hemogram showed that WBC, RBC, and HCT values were significantly lower in infected dogs (the p-value of the first one is $p<0.001$, other two ones are $p<0.05$) compared to healthy controls. The infected dogs had non-significantly lower NEU, EOS, and PLT values, and higher LYM, MON, MCV, MCH, and MCHC values than control group ($p>0.05$). Although the hemolysis rate of infected dogs' erythrocytes at the concentrations of 0.4 - 0.1 % NaCl were higher than that of healthy dogs, this difference was statistically significant at only 0.3% NaCl ($p<0.05$). In addition, the median corpuscular fragility (MCF), equal to the NaCl concentration that lyses 50% of erythrocytes, of dogs with CPVe (0.42%) was higher than the MCF values of the control group (0.39%), but not statistically significant ($p>0.05$). In conclusion, besides the hematological findings revealed that WBC, RBC, and HCT values were significantly lower in dogs with CPVe than that in healthy dogs in this study, it was reported for the first time that canine parvovirus significantly increased osmotic fragility of RBCs at 0.3 % NaCl concentration compared to the control group. We concluded that to consider of these, particularly affected, blood parameters may be useful for determining the prognosis of CPVe.

Keywords: Canine parvovirus, erythrocyte osmotic fragility, hematological parameters.

INTRODUCTION

Canine Parvoviral Enteritis (CPVe) is a viral contagious disease that is highly effective among the puppies at 1.5-6 months old ages throughout the world (Decaro et al., 2007). In dogs with clinical symptoms such as diarrhea, vomiting, and fewer, it has been reported that CPVe has various prevalence between 23.6 and 99.2 %, which was 66 % in Türkiye (Dik and Şimşek, 2021; Pekmezci and Çolak, 2021). Two main factors are responsible for CPVe infection in dogs, which are canine parvovirus Typ-1 (CPV type-1) and Typ-2 (CPV type-2). Although the former leads to disease in neonatal period, the latter is more precisely associated with classic parvoviral enteritis infection (Couto and Nelson, 2009). It has been also reported that CPV type-2 has three subtypes, which are CPV-2a, CPV-2b and CPV-2c, which were transmitted by a fecal-oral pathway in dogs (Pollock and Coyne, 1993; Carr-Smith et al., 1997; Couto and Nelson, 2009). The virus is replicated in oropharynx and local lymphoid tissues, and then passed across to systemic circulation (Prittie, 2004). It mostly heads for rapidly divided lymphoid tissue cells, intestinal crip epithelial cells, bone marrow pioneering cells, and myocardiocytes in pups less than 1 month (Goddard and Leisewitz, 2010). While the demolition of myeloprolifarative cells in the bone marrow and necrosis in the lymphoid tissue resulted in lymphopenia and even panleukopenia in advanced cases, the loss of villus and damage in intestinal mucosa causes malabsorption, hemorrhagic gastroenteritis, endotoxemia and septicemia (Pollock and Coyne, 1993; Carr-Smith et al., 1997; Otto et al., 1997; Tuteja et al., 2022). In most of myocarditis cases, pups can die without clinical findings (Prittie, 2004). The severity of the clinical symptoms in CPVe may vary depending on the age, vaccination, immune system, virulence of the agent and other seconder pathogens in puppies (Couto and Nelson, 2009). Nonspecific symptoms such as anorexia, depression and fever are observed at the beginning of the disease, while the most remarkable clinical finding is vomiting, and especially hemorrhagic diarrhea resulted from small intestine (Macintire and Smith-Carr, 1997). Furthermore, it has been reported that mortality increased up to 91% in cases where patients are not treated in experimental infected puppies (Kariuki Njenga et al., 1990).

Blood is an important body fluid to investigate the physiological and pathological changes in an organism. Therefore, it is used to evaluate the health status and treatment processes in human and animals (Ariyibi et al., 2002; Terzungwe, 2018). Even though it is not specifically identified the reasons for enteric diseases by only hematological parameters, it is possible to get clinically critical knowledge about differential diagnosis, treatment,

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and prognosis (Goddard et al., 2008). Erythrocyte osmotic fragility (EOF) is usually used to estimate the membrane fragility of RBCs in order to evaluate blood-related disorders such as chronic or recurring anemia. EOF is rarely used in routine hematological analysis by clinicians, however, erythrocytes may be affected in many diseases by changing fragility (Slappendel, 1998). It has been previously reviewed that hereditary spectrin deficiency and stomatocytosis, immune-mediated hemolytic anemia and some other anemias in dogs cause increased EOF (Tritschler et al., 2016). Dogs infected with CPVe may develop anemia due to hemorrhagic diarrhea.

According to our current data, although there are few studies reporting the effects of CPVe on blood parameters (Ariyibi et al., 2002; Biswas et al., 2005; Castro et al., 2013; Bhargavi et al., 2017; Dash et al., 2017; Terzungwe, 2018; Khare et al., 2020; Ukwueze et al., 2020; Patel et al., 2022), we could not find specific research regarding erythrocyte status in CPVe. Therefore, in this study, we aimed to investigate the alterations of erythrocyte osmotic fragility accompanied with hematological parameters of parvoviral enteritis in puppies.

MATERIALS AND METHODS

Animals and study design

This study was conducted with the permission of the Kirikkale University Local Ethics Committee for Animal Experiments with the decision number 2022/01 – 4, dated January 10, 2022. 16 healthy and 27 diarrheic dogs (some of them were hemorrhagic diarrhea) presented at Kirikkale University Animal Hospital were analyzed. The number of the animal used in this study determined according to similar previous studies (Castro et al., 2013; Bhargavi et al., 2017; Terzungwe, 2018; Patel et al., 2022; Kurtdere et al., 2023). The healthy dogs brought to the hospital for vaccination program identified as control group which were 2-6 months old and have no clinical symptoms. The other dogs at ages 2-6 months old have some clinical symptoms such as diarrhea, vomiting, anorexia, dehydration, and fewer were checked from stool via rapid Scan Vet Parvo –immunochromatographic kit (CPV Ag Test Kit, BIONOTE, Korea) in order to diagnosis of canine parvovirus infection. The puppies have positive test results were identified as infected dogs and included the study. All the dogs in both groups were mix breed and gender.

Blood sampling and analysis

For the hematological analysis, 3 mL whole blood samples were collected from *Vena Saphena medialis* into the test tubes with anticoagulant - K_3-EDTA. Blood samples were analyzed for hematological parameters as white blood cells (WBC), neutrophil (NEU), lymphocyte (LYM), monocyte (MON), eosinophil (EOS), basophil (BAS), red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), and platelet (PLT) using an auto analyzer (Abacus Junior Vet -5, Austria).

Erythrocyte osmotic fragility test

Following the complete blood analysis, samples were used for erythrocyte osmotic fragility (EOF) test as described in previous reports (Olayemi et al., 2009; Kabakci et al., 2022), with some modification. For this purpose, it was initially prepared various concentrations of sodium chloride (NaCl) as 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, and 0.0% in individual tube containing 10 mM sodium phosphate buffered solution (PBS). Ten microliters (10 µL) volume of whole blood were added into each tubes containing 2.5 mL PBS-NaCl dilutions and incubated for 30 min at laboratory temperature. Samples were then centrifuged at 1000 g for 10 min, in order to obtain supernatants. Afterwards, the optical density of supernatants was measured through a spectrophotometer (Multiskan Go, Thermo Scientific, Finland) at 540 nm. Erythrocyte hemolysis rates of each sample were assessed by comparing with those in distilled water which was assumed to be 100% hemolysis using the formula: % hemolysis = (absorbance of test tubes/absorbance of 0% NaCl dilution tube) x 100. The results were expressed as % hemolysis. It was also determined the median corpuscular fragility (MCF) from the fragility curve, which is equal to the NaCl concentration leading hemolysis 50 percent of erythrocytes, to compere between healthy and infected dogs.

Statistical analysis

Descriptive and statistical analysis the data obtained from this study were performed with SPSS 20.0 package program (IBM, SPSS software for statistics, USA) by using Student's T-test and Mann Whitney U test in line with the result of normality tests for parametric and non-parametric data, respectively. All the data were presented mean with standard error mean (SE). The threshold of P-value is considered as 0.05 for statistical significance.

RESULTS

In the present study, 13 hematological parameters were evaluated in 16 healthy and 27 infected dogs with canine parvoviral enteritis. As seen in Table 1, all the parameters of dogs used as control group were in the range of reference values. When the findings of hemogram were compared between control (healthy) and infected dogs, it was observed that WBC, RBC, and HCT values were significantly lower in infected dogs (the p-value of the first one is $p<0.001$, other two ones are $p<0.05$) than that of control group. HGB values in infected dogs were also intended to be lower than in healthy dogs, but the p value for this parameter was over the statistical threshold ($p=0.069$). Although the infected dogs had lower NEU, EOS, and PLT values, and higher LYM, MON, MCV, MCH, and MCHC values than control group, this difference was not statistically significant ($p>0.05$).

Hematological alterations observed in infected dogs with parvoviral enteritis were summarized in Table 2. The most frequent changes were leucopenia and anemia which were 44,4% and 40,7%, respectively. The percentage of alterations were in the range of 25-34% for lymphocytosis, lymphopenia, neutrophilia, and eosinopenia. Although none of the infected dogs had thrombocytopenia (0/27), six of 27 dogs had thrombocytosis in hematological analysis (22,2%).

Figure 1 shows the erythrocytes osmotic fragility curve at different NaCl concentrations. NaCl concentrations were in the range from 0.9% to 0.0% to provide for red blood cells an environment ranges from isotonic to hypotonic. There was no hemolysis in erythrocytes of both groups (control and infected) at the concentrations of NaCl between 0.9 and 0.5%. Initial and complete hemolysis for all dogs were observed at 0.4% and 0.2% NaCl solutions, respectively. Although the hemolysis rate of infected dogs' erythrocytes at the concentrations of 0.4 - 0.1% NaCl were higher than that of

healthy dogs, this difference was statistically significant at only 0.3% NaCl ($p<0.05$).

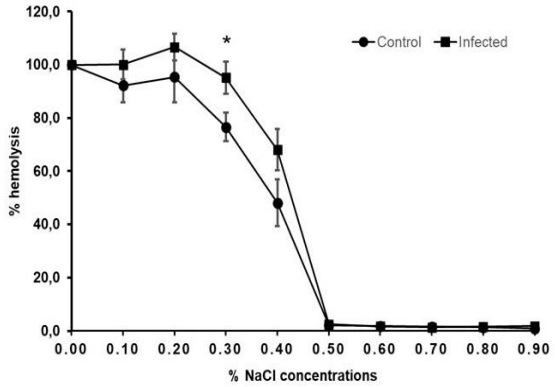

Figure 1. Erythrocyte osmotic fragility curve of 6 healthy (control) and 10 infected dogs with canine parvoviral enteritis in different sodium chloride (NaCl) concentrations. Results were expressed as a percentage of total hemolysis. Asterisks (*) is $p<0.05$.

We also compared the median corpuscular fragility (MCF), which is equal to the NaCl concentration leading to hemolysis 50% of erythrocytes, between two groups (Figure 2). The MCF value of infected dogs (0.42% NaCl) was higher than that of control group (0.39% NaCl) which means that erythrocytes of dogs with parvoviral enteritis have been hemolyzing earlier than that of healthy dogs. However, this difference was statistically non-significant ($p>0.05$).

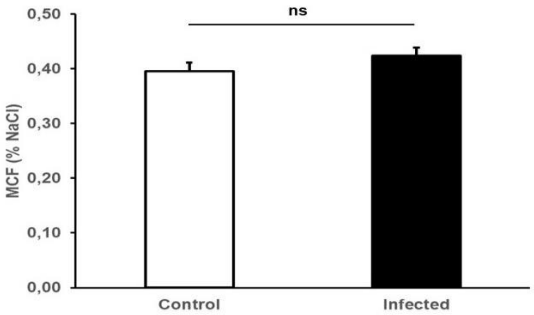

Figure 2. Representative bar graph of median corpuscular fragility (MCF) of erythrocytes from 6 healthy (control) and 10 infected dogs with canine parvoviral enteritis. ns: non-significant. $p>0.05$.

Table 1. Hematological parameters of healty and infected dogs with canine parvoviral enteritis.

Groups	Reference values	Control (n=16) Mean ± SE	Infected (n=27) Mean ± SE	p value
WBC (10^3/µL)	6.0 – 17.0	12.0 ± 0.6	7.8 ± 1.1	**0.006**
NEU (%)	52.0 – 81.0	69.3 ± 3.2	63.3 ± 4.6	0.355
LYM (%)	12.0 – 33.0	22.4 ± 3.1	25.8 ± 4.6	0.600
MON (%)	2.0 – 18.0	4.6 ± 0.5	7.6 ± 1.7	0.191
EOS (%)	0.5 – 1.0	2.9 ± 0.5	2.6 ± 1.0	0.873
BAS (%)	0.0 – 1.3	0.8 ± 0.1	0.7 ± 0.2	0.640
RBC (10^6/µL)	5.1 – 8.5	6.3 ± 0.3	5.4 ± 0.3	**0.037**
HGB (g/dL)	11.0 – 19.0	12.9 ± 0.5	11.3 ± 0.6	0.069
HCT (%)	33.0 – 56.0	38.5 ± 1.5	33.2 ± 1.7	**0.039**
MCV (fL)	60.0 – 76.0	61.2 ± 0.9	61.7 ± 1.2	0.772
MCH (pg)	20.0 – 27.0	20.6 ± 0.3	20.9 ± 0.4	0.569
MCHC (g/dL)	30.0 – 38.0	33.5 ± 0.2	33.9 ± 0.2	0.263
PLT (10^6/µL)	117.0 – 490.0	379.5 ± 25.8	363.4 ± 25.8	0.682

Table 2. Hematological changes in 27 infected dogs with canine parvoviral enteritis.

Hematological alterations	Dogs number with hematological alterations / Infected dogs' number	Percentage of dog's number with hematological alterations (%)
Anemia	11/27	(40,7%)
Leucopenia	12/27	(44,4%)
Leukocytosis	3/27	(11,1%)
Neutropenia	4/27	(14,8%)
Neutrophilia	8/27	(29,6%)
Lymphopenia	8/27	(26,6%)
Lymphocytosis	7/27	(25,9%)
Monocytopenia	3/27	(11,1%)
Monocytosis	3/27	(11,1%)
Eosinopenia	9/27	(33,3%)
Eosinophilia	3/27	(11,1%)
Thrombocytopenia	0/27	(0,0%)
Thrombocytosis	6/27	(22,2%)

DISCUSSION AND CONCLUSION

Canine parvoviral enteritis is a global viral disease which has quite high morbidity and mortality in puppies at ages under 6 months old Although it is common to observe some non-specific clinical symptoms such as anorexia, depression, lethargy in disease initially, severe vomiting and diarrhea, particularly hemorrhagic diarrhea, are typical signs seen in the later stages of CPVe. The virus is able to affect the gastrointestinal system (small intestine), lymph nodes, heart (myocardiocytes), and bone marrow, which lead to changes in some blood parameters (Goddard and Leisewitz, 2010; Khare et al., 2020).

The most frequently observed hematological abnormalities in CPVe were anemia and leukopenia. Compatible with this knowledge, we found in this study that WBC, RBC, and HCT were significantly lower in dogs with CPVe compared to healthy group. Although mean values of these parameters in reference interval, the percentage of leukopenia and anemia among the infected dogs were 44.4% and 40.7%, respectively. In addition, average total leukocyte count was 2.8 thousand per microliter in dogs with leukopenia, and anemic dogs with CPVe had 4.1 million erythrocytes per microliter blood. The HGB values was also lower in infected dogs compared to control groups, but this difference was not statistically significant. Previous studies conducted with CPVe in different countries have been also reported similar results (Castro et al., 2013; Terzungwe, 2018; Khare et al., 2020; Ukwueze et al., 2020). The findings of Khare et al., (2020), were compatible with our results, in which CPVe decreased the RBC, HGB, and PCV values in affected dogs by the side of normal dogs. In other studies, percentage of anemia among the CPV positive dogs have been reported as 57.1% (Bhargavi et al., 2017), and 61.5% (Castro et al., 2013). Anemia is a common finding in CPVe, especially in advance cases, which may be resulted from blood loss with gastric and intestinal hemorrhages and/or depressed erythropoiesis in bone marrow by CPV (Biswas et al., 2005; Khare et al., 2020). On the other hand, Patel et al. (2022), revealed that there was insignificant difference in mean values of Hb, PCV and RBCs in CPV affected and healthy dogs. This is probably due to the fact that dogs are in the early stages of the disease. Our findings on MCV, MCH, MCHC values of infected dogs were statistically similar with normal dogs, which were 61.7, 20.9, and 33.9%, respectively, and in accordance with the report of (Patel et al., 2022).

Common findings in CVPe in terms of leukocytes are leukopenia, lymphopenia, and neutropenia (Goddard et al., 2008). In case of comparison with the control group, we observed that only WBC was significantly lower in infected dogs. However, percentage of monocytopenia, neutropenia, lymphopenia, and eosinopenia among the dogs with CPVe were in range from 11.1 – 33.3% as seen in Table 2. There are many compatible and incompatible reports in the literature with our findings (Biswas et al., 2005; Castro et al., 2013; Bhargavi et al., 2017; Dash et al., 2017; Terzungwe, 2018; Khare et al., 2020; Ukwueze et al., 2020; Patel et al., 2022). The reduced WBC and subtypes of leukocytes are associated with higher affinity of parvovirus to lymphatic tissues and death of hematopoietic progenitors of different types of leukocytes in bone marrow, thymus, lymph nodes and spleen (Goddard et al., 2008), while normal or increased leukocyte levels are explained by the fact that samples were taken at the early stage of the disease (Ukwueze et al., 2020) or secondary bacterial infection (Dash et al., 2017).

In our findings, PLT was not statistically different between healthy and infected dogs. In addition, six of twenty-seven dogs with CPVe had thrombocytosis (22.2%) while none of them had thrombocytopenia. Thrombocytopenia is one of the expected findings of CPVe as revealed in previous studies (Castro et al., 2013; Bhargavi et al., 2017). However, similar to our results, in some other studies (Surendhar et al., 2018; Terzungwe, 2018; Ukwueze et al., 2020; Patel et al., 2022), it has been showed that there was no difference in PLT values between healthy and affected dogs. This may be resulted from the lower level of hemorrhagic diarrhea among the infected dogs in this study, which means that there is no loss of platelet.

The mortality rate of CPVe is rising in the later stages of cases, due to the mostly severe leukopenia and anemia (Patel et al., 2022). Therefore, it is critical to detect the disease as early as possible. Erythrocyte osmotic fragility is affected in many blood-related disorders such as anemia. Hematological parameters as well as EOF are not sufficient to specifically identify illness, but they can supply clinically vital knowledge about differential diagnosis, treatment and prognosis (Goddard et al., 2008). In this study, initial and complete hemolysis for all dogs were at concentrations of 0.4% and 0.2% NaCl, and MCF values of healthy and infected dogs were 0.39% and 0.42% of NaCl, respectively.

The EOF curve of healthy dogs obtained from this study is relatively in agreement with previous studies (Arikan et al., 2004; Behling-Kelly and Collins-Cronkright, 2014). However, there is no specific study investigate the erythrocyte membrane resistance in dogs with CPVe. Therefore, this is the first research presented alterations EOF in canine parvoviral enteritis. According to our findings, although a similar EOF curve was seen in healthy and infected dogs, erythrocytes of dogs with CPVe was significantly more fragile at the concentration of 0.3% NaCl than that of healthy control. The main reason for this may be non-regenerative anemia caused by suppressive effects of CPV to production of RBC on bone marrow, which means circulating erythrocytes are mostly mature and so more fragile in affected dogs (Makinde and Bobade, 1994). It is well known that erythrocytes are more vulnerable to rupture due to the increased oxidative stress (Tyan, 1982). Therefore, oxidative stress may also responsible increased fragility of erythrocytes in dogs with CPVe, since previously revealed that this disease increased blood malondialdehyde level (Kurtdere et al., 2023) and high MDA levels may be associated with cellular membrane damage (Kabakci et al., 2022). Another possible reason of increased fragility may be affected lipid profile of infected dogs. Cell rigidity is closely related to the ratio of phospholipid to cholesterol in cell membranes. The inadequate ability of RBCs to synthesize cholesterol and remove it from their membranes makes erythrocytes particularly susceptible to modification of membrane by plasma lipoproteins (Suda et al., 2002). Behling-Kelly and, Collins-Cronkright, (2014) demonstrated that EOF increased in hyperlipidemic dogs. On the other hand, Yilmaz and Senturk, (2007) reported that dogs with CPVe had lower cholesterol and higher triglyceride levels than that of healthy dogs. In addition, Kurtdere et al., (2023) have showed that significant increases in high-density lipoprotein, cholesterol and triglyceride levels were

determined in CPV infected dogs. In this context, possible hyperlipidemia caused by CPV may be increased EOF in dogs with CPVe.

In conclusion, the data obtained from this study investigating the alterations of hematological parameters and erythrocyte osmotic fragility in canine parvoviral enteritis have revealed that WBC, RBC, and HCT values were significantly lower in dogs with CPVe than that in healthy dogs, contrary to the other unchanged blood parameters showed in Table 1. This study also reported for the first time the findings of the assessment of EOF in CPVe that canine parvovirus increased osmotic fragility of RBCs at 0.3% NaCl concentration. It was concluded that mature erythrocytes resulted from suppressed bone marrow, increased oxidative stress, and/or hyperlipidemia as in detail discussed above might be responsible for these alterations. In addition, to consider of these, particularly affected, blood parameters may be useful for determining the prognosis of CPVe.

Conflict of Interest

The authors declared that there is no conflict of interest.

Authorship contributions

Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, and Writing took placed by R.K. and E.K.

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Ethical Approval

This study was conducted with the permission of the Kirikkale University Local Ethics Committee for Animal Experiments with the decision number 2022/01 – 4, dated January 10, 2022.

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