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Effect of Ozonized saline solution on oxidative stress in cats with Feline Infectious Peritonitis

Efecto de la solución salina ozonizada sobre el estrés oxidativo en gatos con peritonitis infecciosa felina

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ABSTRACT

Feline infectious peritonitis is a viral disease in cats characterized by systemic involvement and a frequently fatal outcome. Diagnosis is established through a comprehensive assessment of clinical signs and laboratory findings. The aim of this study was to evaluate the efficacy of a single intravenous administration of 100 mL of 0.9 % isotonic sodium chloride solution, ozonated at a concentration of 5 µg/mL for 5 minutes using the Vetozone Medical Ozone Device, on oxidative stress parameters and survival time. In this context, oxidative stress markers were compared before and after treatment to provide scientific data on the potential therapeutic effects of ozonated saline in veterinary medicine. The study was conducted on a sample of 10 domestic cats diagnosed with Feline infectious peritonitis, all of which were monitored for a follow-up period of 6 months to assess clinical progression and survival. In the study conducted on cats diagnosed with Feline infectious peritonitis, administration of ozonated saline resulted in increased total antioxidant capacity and native thiol levels, accompanied by decreases in total oxidant capacity, oxidative stress index, and disulfide levels at the 1-hour mark. Although these changes were not statistically significant ($P > 0.05$), the findings suggest that ozone exerts a regulatory effect on oxidative stress and helps restore the thiol–disulfide balance toward an antioxidant state. In addition, the treatment markedly improved clinical signs, reduced oxidative stress markers, and achieved a 100 % survival rate in the treated cats. These results indicate that ozonated saline solution, by reducing free radical–induced cellular damage in cats with Feline infectious peritonitis, has the potential to be used as a supportive (adjuvant) approach rather than as a directly curative therapeutic agent. Nevertheless, larger controlled clinical studies with extended follow-up periods are required to validate these effects and to standardize the therapeutic protocol.

Key words: Cat; Feline infectious peritonitis; oxidative stress; ozone; reverse transcription-polymerase chain reaction; Türkiye.

RESUMEN

La peritonitis infecciosa felina es una enfermedad viral caracterizada por afectación sistémica y un pronóstico frecuentemente fatal. El diagnóstico se establece mediante una evaluación exhaustiva de los signos clínicos y de los hallazgos laboratoriales. El objetivo de este estudio fue investigar la eficacia de una única administración intravenosa de 100 mL de solución de cloruro de sodio al 0,9 %, ozonificada a 5 µg/mL durante 5 minutos mediante el dispositivo Vetozone Medical Ozone, sobre los parámetros de estrés oxidativo y el tiempo de supervivencia. Para este fin, se compararon los marcadores de estrés oxidativo antes y después del tratamiento, con el propósito de aportar datos científicos sobre el valor terapéutico de la solución salina ozonificada en medicina veterinaria. El estudio incluyó 10 gatos domésticos diagnosticados con peritonitis infecciosa felina, seguidos clínicamente durante seis meses para evaluar la evolución y supervivencia. Tras la administración de solución salina ozonificada, se observó un incremento en los niveles de capacidad antioxidante total y de tiol nativo, acompañado por reducciones en capacidad oxidante total, índice de estrés oxidativo y disulfuro a la hora posterior al tratamiento. Aunque dichas variaciones no alcanzaron significación estadística ($P > 0,05$), los resultados sugieren que el ozono podría ejercer un efecto modulador sobre el estrés oxidativo, favoreciendo la restauración del equilibrio tiol–disulfuro hacia un estado antioxidante. Además, se evidenció una mejoría notable de los signos clínicos, una disminución de los marcadores de estrés oxidativo y una tasa de supervivencia del 100 % en los animales tratados. Estos resultados indican que la solución salina ozonificada, al reducir el daño celular inducido por radicales libres en gatos con peritonitis infecciosa felina, tiene el potencial de utilizarse como un enfoque de apoyo (adyuvante) más que como un agente terapéutico directamente curativo. No obstante, se requieren investigaciones clínicas controladas, con muestras más amplias y períodos de seguimiento prolongados, para confirmar estos efectos y establecer protocolos terapéuticos estandarizados.

Palabras clave: Gato; peritonitis infecciosa felina; estrés oxidativo; ozono; reacción en cadena de la polimerasa con transcripción inversa; Türkiye.

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INTRODUCTION

Feline coronaviruses (FCoV) belong to the Coronaviridae family and are biologically divided into two subtypes: Feline Enteric Coronavirus (FECV) and Feline Infectious Peritonitis Virus (FIPV) [1]. FECV is mostly considered a non-pathogenic strain, causing only mild cases of diarrhea [2].

In contrast, Feline Infectious Peritonitis (FIP), a pathogenic strain, is a systemic and often fatal infectious disease [1 , 3]. The disease can occur in three clinical forms: effusive (wet), noneffusive (dry) and mixed [3 , 4].

The effusive (wet) form of FIP is characterized by fluid accumulation in body cavities (such as the abdomen, chest or pericardium) and is the most common clinical form. In contrast, the non-effusive (dry) form is characterized by neurological symptoms (e.g. paralysis, seizures, head shaking), systemic symptoms (fever, anorexia, weight loss, malaise, weakness, rarely jaundice) and organ involvement (such as granulomas in the kidneys and lesions in the lungs) [4 , 5].

The lack of a single specific and definitive diagnostic test for FIP complicates the diagnosis. Therefore, the diagnosis is supported by a combination of clinical symptoms and laboratory methods such as enzyme-linked immunosorbent assay (ELISA), virus neutralization tests, molecular analyses [1 , 6 , 7 , 8 , 9 , 10]. Furthermore, hemogram and various biochemical parameters also provide valuable information in the differential diagnosis of FIP [1 , 11].

Different results have been reported in hematologic and biochemical studies in cats (*Felis catus*) with FIP [1 , 12]. The most commonly reported hematologic findings in FIP cases include mild anemia, lymphopenia and thrombocytopenia. It has been reported that approximately 65 % of cats with FIP develop anemia. In patients with FIP, hematocrit values usually fall below 30 % and decreased hemoglobin levels can be observed [6 , 9 , 12 , 13 , 14].

In biochemical analysis, one of the most common laboratory findings in cats with FIP is hyperglobulinemia, which is observed in approximately 40-60 % of cases [6 , 12 , 13 , 15]. The increase in total protein levels is due to an increase in plasma antibody concentration, mainly in the gamma-globulin fraction, and a decrease in albumin levels [9]. Not only increased globulin levels but also decreased albumin levels are typical in cats with FIP [6 , 14 , 16].

Liver failure or increased vascular permeability can lead to low albumin and consequently a reduced albumin/globulin (A/G) ratio. A/G ratio below 0.8 is considered a high-risk indicator for FIP, with a diagnostic accuracy of 92 % at this threshold. In contrast, an A/G ratio above 0.8 significantly reduces the likelihood of FIP [6 , 12 , 15].

The FIP virus selectively infects monocytes and macrophages, the main defense cells of the immune system, and actively replicates in these cells [1]. The replication of the virus in these cells triggers excessive release of cytokines, leading to an intense and uncontrolled immune response. In this process, especially through proinflammatory cytokines, the production of reactive oxygen species (ROS) increases and oxidative stress develops as a result [17].

Oxidative stress causes damage to cell structures, contributing to disruption of physiological balance, damage to the interaction between the immune system and tissue, and worsening of the course of the disease [17 , 18].

In this context, ozone therapy has been investigated since the late 20th century due to its positive effects on redox balance. Ozone is defined as a powerful oxidant that triggers the production of ROS when it comes into contact with biological fluids. These molecules accelerate tissue regeneration by stimulating cellular metabolism and also show antibacterial and antiviral effects [19 , 20 , 21].

The antiviral effect of ozone is associated with oxidative damage to phospholipid and glycoprotein structures in the virus membrane, disruption of viral integrity and inhibition of replication [22 , 23]. However, ozone cannot directly inactivate intracellular pathogens; instead, it indirectly stimulates the immune system, producing a protective effect through neutrophil activation and cytokine release [24 , 25].

In clinical applications, ozone is successfully used as supportive therapy, especially in cases of resistant infections, slow-healing lesions and poor epithelialization. Examples include diabetic ulcers, feline immunodeficiency virus (FIV) infections and chronic wound healing in horses (*Eqqus caballus*) [26 , 27]. It is known that oxidative stress plays an important role in the pathogenesis of FIP and antioxidant defense systems are insufficient in this process.

This situation facilitates the progression of the disease and aggravates the clinical picture. In this context, ozonated saline solution with its immune-modulating (immunomodulatory) and oxidative damage-reducing (antioxidant) effects draws attention as an alternative supportive treatment option in addition to traditional therapies [26]. This study was planned to investigate the effects of ozonated saline application on oxidative stress levels in cats diagnosed with FIP.

MATERIALS AND METHODS

Ethical statement

This study was conducted with permission from the Local Ethics Committee for Animal Experiments of the Samsun Veterinary Control Institute, under the letter dated 22.11.2024 with reference number 19572899/031-90. (Decision no: 2024/08).

Collection of samples

This study included 10 domestic cats presented to Pati Veterinary Clinic in Samsun in 2024 with a preliminary diagnosis of FIP, confirmed by clinical and laboratory evaluations. In accordance with international ethical standards and the 3R (Replace, Reduce, Refine) principles, no control group was established.

The creation of a placebo or untreated control group was considered ethically inappropriate due to the high mortality rate and progressive nature of FIP, as withholding a potentially beneficial intervention could compromise animal

welfare. Therefore, the study design prioritized both scientific validity and ethical responsibility, enabling the collection of preliminary data regarding the potential therapeutic effects of a single intravenous administration of ozonated saline solution. Observed clinical signs included lethargy, anorexia, weight loss, respiratory distress, ocular lesions, high fever, fluid accumulation, and neurological symptoms.

In cases with a preliminary diagnosis of FIP, demographic and clinical data, including sex, breed, age, disease form (effusive/non-effusive), and response to treatment, were collected and are presented in TABLE I. Clinical findings observed in FIP-suspected cats included lethargy, anorexia, weight loss, respiratory distress, ocular lesions, high fever, fluid accumulation in the thoracic and abdominal cavities, and neurological symptoms.

TABLE I
Distribution of Breed, Age, Gender, Clinical Form and Response to Treatment in Cats with Feline Infectious Peritonitis Admitted to the Veterinary Clinic

Patient Number	Race	Age (Month)	Gender	Form of the Disease	Response to treatment
1	British Shorthair	8	Female	Efusiv Form	Alive
2	Tabby	5.5	Female	Non-Effusive Form	Alive
3	Scottish Fold	1.5	Male	Efusiv Form	Alive
4	Tabby	5	Male	Non-Effusive Form	Alive
5	Tabby	10.5	Female	Non-Effusive Form	Alive
6	British Shorthair	10	Female	Efusiv Form	Alive
7	Tabby	10	Female	Non-Effusive Form	Alive
8	Tabby	15	Male	Non-Effusive Form	Alive
9	Tabby	13	Male	Efusiv Form	Alive
10	Tabby	8	Female	Efusiv Form	Alive

The study material consisted of cats diagnosed with FIP based on clinical signs, Nested RT-PCR, hematological and serum biochemical analyses, and ultrasonographic examination. Blood samples were collected from the antebrachial cephalic vein; 4 mL samples were used for biochemical analyses and 1 mL for hematological analyses. Whole blood was analyzed shortly after collection using an automatic hematology analyzer, and biochemical tests were performed the same day with an automatic biochemistry analyzer. Samples were centrifuged (Nüve, CN 180, Türkiye) at 1000 g for 15 minutes (min) to obtain serum, which was stored in a deep freezer (Arçelik, 2041 Nd, Türkiye) -20 °C for oxidative stress analysis. Serum samples were collected at treatment initiation, 1 hour (h) post-treatment, and 2 days (d) post-treatment.

Ultrasounde examination

Radiographic evaluation (DR TECH, EXPRIMER, South Korea) revealed pleural effusion in the thoracic cavity and free fluid accumulation in the abdominal region. This widespread effusion pattern is considered a typical finding consistent with systemic diseases, particularly the effusive (wet) form of FIP (FIG. 1A). Abdominal ultrasonography (CHISON EBIT 60, China) revealed a hyperechoic line in the renal medulla, known as the 'renal medullary rim sign' (FIG. 1B). This ultrasonographic finding has been reported in some infectious and inflammatory processes, particularly FIP, and is considered a non-specific but noteworthy sign.

Rivalta test

A sterile tube containing 100 mL of distilled water and 1 drop of 98 % acetic acid was mixed homogeneously, and one drop of effusion fluid was carefully added to the prepared solution. The effusion drop remaining suspended in the solution without dispersing was considered a positive result (FIG 2C). This finding is an important diagnostic criterion in the characterisation of effusion and serves as a clinically meaningful indicator for distinguishing between transudate and exudate in pleural and/or peritoneal fluids associated with inflammatory or infectious aetiology. In the effusive (wet) form of FIP, the presence of exudate-type fluids with high protein content and a viscous character is characteristic. Therefore, a positive test result can be considered a supportive finding for the possibility of FIP.

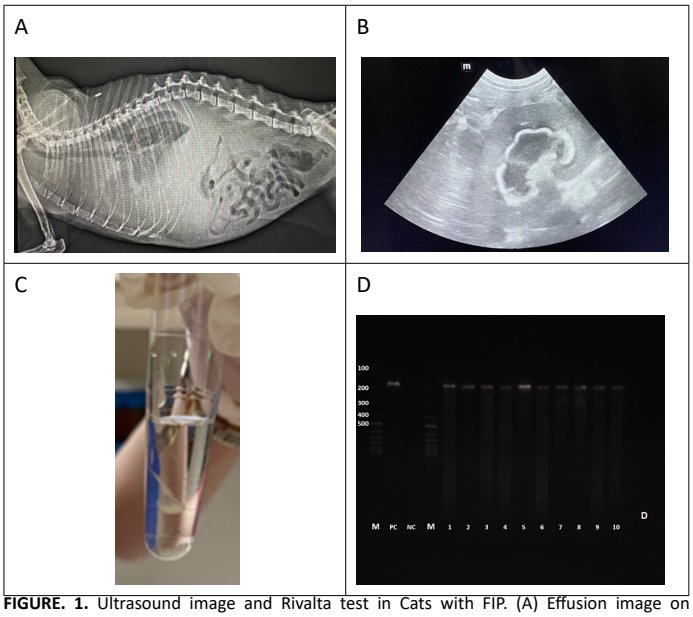

FIGURE. 1. Ultrasound image and Rivalta test in Cats with FIP. (A) Effusion image on thoracoabdominal radiography. (B) Renal medullary rim sign image. (C) Positive Rivalta test (All images have been obtained from cases included in this study). (D) Nested RT-PCR gel images of Feline Infectious Peritonitis.

Hematologic analyzes

In hematological analyses, total leukocyte (WBC) count, granulocyte (GRA), monocyte (MID), lymphocyte (LYM) counts and percentages, platelet (PLT) and erythrocyte (RBC) counts were measured from blood samples containing K3EDTA. In addition, hemoglobin (Hb) concentration, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were also determined in blood samples with a blood analyzer (Mindray BC60R Vet HI-END Laser & Fluorescent Hemogram Device, China).

Biochemical analyses

In biochemical analyses, total protein (TP), albumin (A), blood urea nitrogen (BUN), creatinine levels and alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) activities were measured by photometric method. These analyses were performed using a biochemistry device (RX Monoco Fully Automated bbott Architect Ci8200 Biochemistry device, USA). In addition, globulin (G) levels were determined by subtracting albumin value from total protein value for each cat and A/G ratios were calculated using these values.

In the evaluation of oxidative stress; total antioxidant capacity (TAS) (Rel Assay), total oxidant capacity (TOS) (Rel Assay), native thiol (Rel Assay) and total thiol (Rel Assay) parameters were measured using calorimetric test kits according to the procedure recommended in the kit. The measurements of the kits used were performed on an ELISA plate reader device. The oxidative stress index (OSI) was calculated based on the obtained TAS and TOS values. Since OSI is calculated as the ratio of TOS to TAS, it is expressed without a physical dimension. The ratio of TOS to TAS:

Disulfide (SS) levels were calculated using native thiol and total thiol measurements. Accordingly, half of the difference between total thiol and native thiol concentrations was recorded as the SS level. These parameters were used to evaluate thiol–disulfide homeostasis.

The principle of the total oxidant capacity colorimetric test kit is based on the formation of a colored complex between iron ion and chromogen in acidic medium. The intensity of the color formed can vary depending on the number of oxidants in the sample. The intensity of this color change is determined spectrophotometrically.

The principle of the Total Antioxidant colorimetric test kit is based on measuring the absorbance of the color change in the dark blue-green ABTS of antioxidants in biological material. The OSI value is calculated after the TAS and TOS data are determined.

The principle of total thiol test kits is that reducible SS bonds are reduced to form free functional thiol groups. The unused reductant sodium borohydride is consumed and removed with formaldehyde and reduced after reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid (DTNB) and all thiol groups including natural thiol groups are determined.

Half of the difference between total thiols and native thiols is recorded as the dynamic SS amount. After determination of natural thiols (SH) and total thiols, SS amounts were calculated.

Molecular analysis

Viral RNA was extracted from plasma samples using the Roche High Pure Viral Nucleic Acid Kit (REF:11858874001, Germany), reverse-transcribed to cDNA with the QIAGEN cDNA Synthesis Kit (01188772, Vilnius, Lithuania), and detected by nested PCR using Thermo Scientific DreamTaq (EP0702, Lot 0124949). The primer sets used were: P205/P211 (223 bp): P205: GGCAACCCGATGTTTAAAACTGG, P211: CACTAGATCCAGACGTTAGCTC; P276/P204 (177 bp): P276: CCGAGGAATTACTGGTCATCGCG, P204: GCTCTTCCATTGTTGGCTCCTCGTC. PCR products were subsequently analyzed by gel electrophoresis [28].

Treatment protocol

During the treatment process, cat owners were provided with both verbal and written information about the ozone therapy that would be administered to their pets in addition to the treatment; informed consent was obtained prior to the application. Because accepted supportive treatment protocols are available for FIP, the deliberate withholding of treatment from diagnosed cats was considered ethically inappropriate. Therefore, an untreated control group was not established in this study. All cases received standard conventional therapy, and additionally, ozonated saline solution was administered as a supportive treatment. The treatment protocol administered to patients includes a complementary ozone therapy application in addition to traditional pharmacological approaches. Within the scope of conventional treatment, prednisolone, known for its anti-inflammatory and immunomodulatory effects, was administered orally (PO) once daily at an initial dose of 2 mg/kg. The dose was reduced to 1 mg/kg in the second week and to 0.5 mg/kg in the third week, with the treatment discontinued at the end of the third week. Additionally, pentoxifylline, preferred for its microcirculatory-enhancing and antioxidant properties, was administered orally once daily at a dose of 10 mg/kg in non-effusive cases and up to 25 mg/kg in effusive cases depending on the clinical condition, and the treatment was maintained for 4 weeks.

In addition to this treatment, Ozone therapy was applied as a supportive method. For this purpose, 100 mL of 0.9 % isotonic sodium chloride solution was ozonated at a concentration of 5 µg/mL for 5 min using the Vetozone Medical Ozone Device. Since the first 48 hours of the disease are considered critical in cats with FIP, the ozonated solution was administered as a single intravenous (IV) dose following diagnosis. The aim was to utilise the potential anti-inflammatory, immunomodulatory and cellular oxygenation-enhancing effects of ozone therapy. This protocol was designed to evaluate the synergistic effects of both conventional and complementary medical approaches.

Statistical analysis

All statistical calculations of the data were performed using SPSS statistics 27 program. Shapiro-Wilk test was used to evaluate whether the data were normally distributed. For the comparison of repeated measures, repeated measures test was applied to the normally distributed data. Friedman test, which is a nonparametric test, was applied to the non-normally distributed data. Data with a P value less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Complete blood count (Hemogram)

As a result of the haematological analyses conducted in the study, mild increases in total leukocyte count, neutrophil count, and monocyte count were observed in cats diagnosed with FIP. This finding was interpreted as an indicator of the inflammatory response associated with the disease. Additionally, total erythrocyte counts and haemoglobin levels were found to be near the lower limit of the reference range, while HCT values were significantly reduced below 30 %. This haematological profile indicates the presence of anaemia in cats with FIP, alongside leukocytosis caused by neutrophils and monocytes. Hemogram findings of the cats with FIP in this study are given in TABLE II.

TABLE II
Analysis of Hematologic Parameters of Cats Diagnosed with Feline Infectious Peritonitis

Parameters	**Value** ± (Mean SD)	**Unite**
WBC	14.848 ± 6.553	($\times10^9$/L)
Neu	11.098 ± 4.486	($\times10^9$/L)
LYM	2.061 ± 1.947	($\times10^9$/L)
Mon	0.660 ± 0.378	($\times10^9$/L)
Eos	1.416 ± 1.428	($\times10^9$/L)
Bas	0.060 ± 0.071	($\times10^9$/L)
Neu %	0.769 ± 0.133	(%)
Lym %	0.135 ± 0.101	(%)
Mon %	0.044 ± 0.025	(%)
Eos %	0.088 ± 0.060	(%)
Bas %	0.004 ± 0.005	($\times10^9$/L)
PLT	304.000 ± 104.001	($\times10^9$/L)
MPV	13.020 ± 1.619	(fL)
PDW	14.010 ± 0.436	(fL)
PCT	3.944 ± 1.435	(%)
IPF	21.150 ± 12.072	(%)
RBC	7.314 ± 1.522	($\times10^{12}$/L)
HGB	9.790 ± 1.739	(g/dL)
HCT	27.660± 5.239	(%)
MCV	38.250 ± 5.244	(fL)
MVH	13.520 ± 1.558	(pg)
MCHC	354.800 ± 19.521	(g/dL)
RDW-CV	0.200 ± 0.030	(%)
RDW-SD	27.000 ± 5.259	(fL)
RET	25.130 ± 13.165	($\times10^9$/L)
RET%	0.350 ± 0.180	(%)
IRF	8.870 ± 6.501	(%)
LFR	91.130 ± 6.501	(%)
MFR	8.690 ± 6.472	(%)
HFR	0.770 ± 0.359	(%)
RHE	16.380 ± 1.141	(pg)

WBC: White Blood Cell count, Neu: Neutrophil count, LYM: Lymphocyte count, Mon: Monocyte count, Eos: Eosinophil count, Bas: Basophil count, Neu %: Neutrophil percentage, Lym %: Lymphocyte percentage, Mon %: Monocyte percentage, Eos %: Eosinophil percentage, Bas %: Basophil percentage, PLT: Platelet count, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, PCT: Plateletcrit, IPF: Immature Platelet Fraction, RBC: Red Blood Cell count, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MVH: Mean Hemoglobin Volume, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW-CV: Red Cell Distribution Width–Coefficient of Variation, RDW-SD: Red Cell Distribution Width–Standard Deviation, RET: Reticulocyte count, RET%: Reticulocyte percentage, IRF: Immature Reticulocyte Fraction, LFR: Low Fluorescence Ratio, MFR: Medium Fluorescence Ratio, HFR: High Fluorescence Ratio, RHE: Reticulocyte Hemoglobin Equivalent

Although various hematologic and laboratory abnormalities have been reported in cats diagnosed with FIP, none of these parameters are pathognomonic [1 , 9 , 29 , 30 , 31 , 32]. In a retrospective study by Riemer *et al.* [33], lymphopenia was found in approximately 49.5 % of patients with FIP, neutrophilia with left shift in 39-57 %, and mild to moderate normocytic normochromic anemia in 37-54 %. Similarly, in this current study, neutrophilia and anemia were found in cats diagnosed with FIP.

These hematologic changes are thought to be a reflection of the physiologic stress on the hemopoietic system associated with the chronic nature of the disease and endogenous stress responses that occur during infection. In the literature, it has been reported that hematocrit levels in FIP patients are frequently below 30 %; the mean hematocrit value of 27.66 % obtained in the study supports these findings [6 , 9 , 13 , 14]. These data contribute to a better understanding of the hematologic profile of FIP.

Biochemical analysis

Biochemical analysis results of the cats with FIP included in the study are given in TABLE III.

TABLE III
Analysis of Biochemical Parameters of Cats Diagnosed with Feline Infectious Peritonitis

Parameters	Values ± (Mean SD)
Urea (mg/dL)	37.02 ± 18.66
Creatinine (mg/dL)	0.83 ± 0.48
Total Protein (g/dL)	9.79 ± 1.89
Albumin (g/dL)	2.67 ± 0.59
Total Bilurubin (mg/dL)	1.48 ± 2.15
Direct Bilirubin (mg/dL)	0.25 ± 0.53
ALT (IU/L)	57.60 ± 51.84
AST (IU/L)	47.04 ± 37.50
ALP (IU/L)	22.00 ± 10.79
Phosphorus (mg/dL)	4.79 ± 1.12
Globulin (g/dL)	7.12 ± 1.80
A/G %	0.39 ± 0.11

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, A/G: albumin/globulin ratio.

Biochemistry analyses performed in the study revealed an increase in total protein level, suggesting that this may be associated with hyperglobulinemia specific to FIP. Albumin level (2.67 ± 0.59 g/dL) was close to the lower limit of the reference range and this is associated with decreased liver synthesis and fluid losses during inflammation. G levels significantly above the reference range (3.4-5.2 g/dL) are indicative of a characteristic outcome for FIP. While an ALB/Glob ratio of < 0.4 supports the diagnosis, this ratio was found to be 0.39 ± 0.11 in the study. Total bilirubin level (1.48 ± 2.15 mg/dL) was found to be above the reference range (0-0.4 mg/dL); this increase is associated with liver damage, hemolysis or bile flow disorders.

Biochemical analyses of cats with FIP show that the disease causes characteristic changes in certain parameters. Among these changes, significant increases in total bilirubin, total protein and globulin levels and significant decreases in albumin levels and A/G ratio [32 , 34].

Studies have revealed that A/G ratio may be an important biochemical indicator in the diagnosis of FIP. Especially in cases where the A/G ratio is > 0.8, the probability of FIP is considered low, while a decrease in this ratio to < 0.4 indicates a high risk for FIP [9 , 31 , 35]. Hartmann *et al*. [15] reported that the probability of FIP increased in cats with an A/G ratio < 0.45, while the disease was largely excluded when the ratio was > 0.8.10 The mean A/G ratio of 0.39 ± 0.11 obtained in this study was consistent with the results of Norris *et al.* [13] and Tsai *et al*. [11] in the literature and supported that this ratio may be a valuable biomarker in the diagnosis of FIP.

In the study, TAS, TOS, OSI, native thiol, total thiol and SS values were determined as important biomarkers in the evaluation of the oxidant/antioxidant balance of the organism. The results are given in TABLE IV and FIG. 2.

TABLE IV

Parameters	0. h	1. h	2. day	P value
TAS (mmolTroloxEq/L)	0.74 ± 0.22	0.87 ± 0.38	0.74 ± 0.28	0.569
TOS (µmol H_2O_2 Eq/L)	46.62 ± 23.85	29.83 ± 16.06	49.36 ± 17.33	0.118
OSI (AU)	64.57 ± 27.87	42.10 ± 27.77	74.94 ± 29.72	0.074
Native thiol (µmoL/L)	160.86 ± 90.51	103.65 ± 61.67	112.09 ± 76.33	0.123
Total thiol (µmoL/L)	427.23 ± 251.45	331.65 ± 233.72	485.19 ± 326.31	0.233
Disulfide (µmoL/L)	133.18 ± 95.02	114.00 ± 120.63	340.28 ± 248.35	0.407

Changes in Total antioxidant capacity, Total oxidant capacity, oxidative stress index, Native thiol, Total thiol and Disulfide serum values according to hours in ozone treated animals (X ± SD).

TAS (Total antioxidant capacity), TOS (Total oxidant capacity), OSI (Oxidative stress index), 0.h (before treatment), 1. h (1 hour after treatment), 2. d (2 day after treatment) Total antioxidant capacity (TAS), Total oxidant capacity (TOS), Oxidative stress index (OSI), native thiol, total thiol and disulfide levels were analyzed in three time periods: before treatment (0th h), 1 h after the start of treatment and on the 2nd d in order to evaluate the effect of ozonized saline solution on oxidative stress parameters in cats diagnosed with FIP. In this study results, no statistically significant difference was found between the groups in terms of TAS, TOS, OSI, native thiol, total thiol and disulfide values (P > 0.05).

However, TAS levels increased while TOS, OSI and SS levels decreased in the 1st h, although it was not statistically significant. TOS level increased due to the natural course of the infection. However, ozone administration prevented excessive increase in TOS levels in the first h after treatment. This suggests that ozone may have a regulatory effect on oxidative stress when used in a controlled manner. The study results show that ozonized saline application increased antioxidant activity and decreased oxidative stress in the 1st h. In addition, an increase in native thiol levels ($P > 0.05$) and a decrease in SS levels ($P > 0.05$) were observed, although not statistically significant, with the strengthening of the antioxidant defense system at 1 h after ozone administration. This shows that the thiol-disulfide balance is restructured in the antioxidant direction and ozone provides a protective effect in this process.

Oxidative stress has been associated with many viral infections in both humans and animals and is usually caused by the action of proinflammatory cytokines released early in the infection. Cats are more susceptible to the development of oxidative stress due to their unique metabolic characteristics. This is due to the limited capacity of their antioxidant system and the role of oxidative stress in the pathogenesis of feline pathogenesis has become an important research topic.

However, studies evaluating the effects of antioxidant supplements in cats are quite limited [17 , 18 , 36]. Webb *et al.* [37] reported that oxidative stress is prominent in cats infected with FIV, which leads to loss of CD4 (+) T lymphocytes. Similarly, other studies in cats with FIV have emphasized the potential therapeutic benefits of antioxidant supplements; however, more controlled studies are needed in this area [38].

To date, there has been no direct study on the role of oxidative stress in the physiopathology of FIP [38 , 39 , 40]. In this respect, the present study is one of the studies aiming to evaluate oxidative stress in cats diagnosed with FIP.

In the study, a statistically significant negative correlation was found between TAS and TOS; this finding coincides with the study of Suresh *et al.* [41] who previously reported low TAS levels in cats with FIV. Similarly, low TAS levels were also observed in this study. However, a significant increase in TAS levels and a decrease in TOS, OSI and SS levels were recorded in the first hour following administration of ozonated saline solution.

These results suggest that ozone treatment may modulate oxidative stress by activating the antioxidant defense system in the short term. However, due to the chronic and progressive course of FIP, a decrease in TAS levels was observed again from d two.

This suggests that the antioxidant capacity of the body becomes insufficient with the progression of the disease and the oxidative load increases again. An increase in TOS levels was observed due to the natural process of the infection.

However, ozone treatment suppressed the sharp rise in TOS in the first h after treatment and showed a regulatory effect in the acute phase of oxidative stress. These findings suggest that controlled ozone administration may be a potential supportive therapy that may stabilize the oxidative stress response in viral diseases such as FIP.

However, it should not be ignored that this effect may be limited in the long term due to the nature of chronic infections.

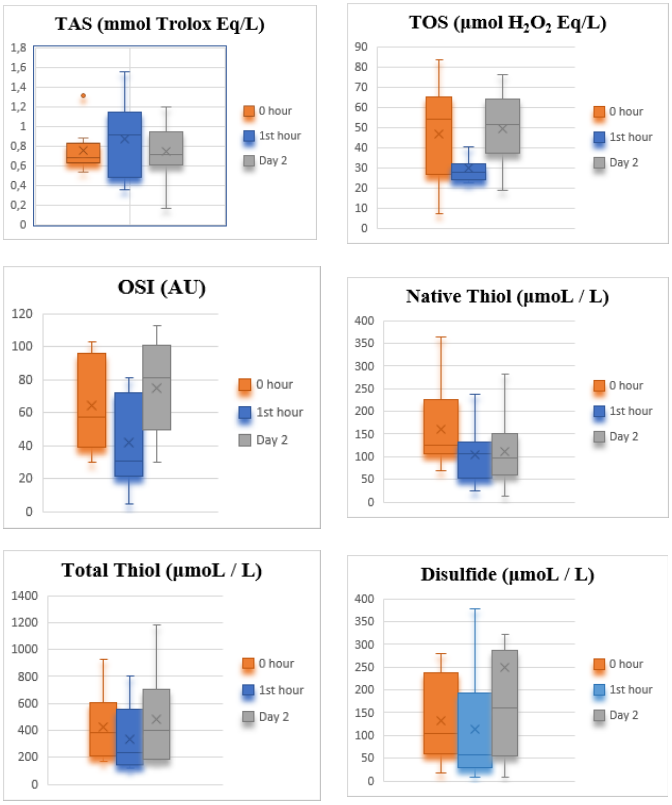

FIGURE 2. Serum TAS (Total antioxidant capacity), TOS (Total oxidant capacity), OSI (Oxidative stress index), Native Thiol, Total Thiol and Disulfide Levels.

Nested RT-PCR

The products obtained by PCR were run using 1.5 % agarose gel electrophoresis and visualized under UV light. The gel was evaluated together with positive and negative controls and the result was considered positive if a band was formed at 177 bp. In the negative control group, no band is expected [28]. The gel image showing the PCR results is presented in FIG.1D.

In recent years, RT-PCR, one of the molecular methods in the diagnosis of FIP, has become an important tool, especially due to its sensitivity for the detection of viral RNA. However, due to the genetic similarities between enteric coronavirus (FECV) and the mutated form causing FIP (FIPV), the use of RT-PCR alone as a differential diagnostic tool remains limited [9 , 28].

Therefore, RT-PCR results should be evaluated together with clinical findings and hematologic/ biochemical parameters. In this study, the diagnosis of FIP was confirmed by RT-PCR and the results were interpreted in an integrated manner with other laboratory findings.

Changes in clinical findings after treatment

Significant improvements were observed in the clinical evaluations of treated patients. In particular, increased appetite

and normalization of mild fever were among the notable findings. A marked increase in the activity levels of patients was detected, and improvement in the color of the mucosal membranes indicated an enhancement in the systemic condition. In addition, notable reductions in effusion-related symptoms were observed; abdominal distension improved significantly, and remarkable improvement in respiratory distress was achieved. These findings were considered strong indicators of a positive clinical response to treatment.

A significant decrease in clinical symptoms was recorded post-treatment, with a 100 % survival rate maintained within the first 48 h of treatment and throughout the subsequent six-month follow-up period. The six-month survival data were obtained from the clinical records of all treated cats and information provided by their owners.

Each cat was monitored after treatment at predefined intervals (1 week, 1 month, 3 months, and 6 months) through regular clinical examinations and direct communication with the owners. During these follow-ups, clinical findings, general health status, and survival were systematically recorded. Throughout the follow-up period, a continuous and consistent improvement in the general health status of the cats was observed, with a marked increase in their quality of life.

Although the sample size was limited, these longitudinal observations reliably demonstrate that all cats survived during the six-month period following ozone therapy. In conclusion, the applied treatment protocol significantly improved the overall health status and quality of life of the patients.

Nevertheless, despite the favorable clinical outcomes obtained, the treatment of FIP remains complex, prolonged, and economically demanding. Therefore, early diagnosis and the implementation of appropriate supportive treatment strategies are of paramount importance to enhance the sustainability of clinical improvement and to maximize therapeutic success [1 , 9 , 42 , 43]. In this context, the present study evaluated the potential contribution of ozonized saline solution, administered in addition to conventional therapy, to oxidative stress parameters and overall treatment efficacy.

Feline infectious peritonitis is a common disease worldwide, reported in North America (USA and Canada), Africa (South Africa and Senegal), Asia (Japan), Oceania (Australia) and several countries in Europe (United Kingdom, Ireland, Netherlands, Germany, Belgium, Switzerland and France) [29]. FIP has long been regarded as a disease with a poor prognosis, characterized by a progressive and often fatal course. Today, FIP remains a serious health problem in cats due to the difficulty of treatment and the inability of current vaccines to provide adequate protection [44]. However, the development of antiviral agents for the treatment of human coronavirus infections has generated new hope for effective and life-saving therapeutic options for FIP. Despite these advances, FIP treatment remains limited in many countries, and in some cases, unlicensed or unregistered antiviral drugs are used [45 , 46 , 47].

Remdesivir, which has been widely used in the treatment of COVID-19, has been evaluated in numerous studies for the treatment of FIP in cats [47 , 48]. Coggins *et al.* [48] reported that 96 % of cats with FIP treated with remdesivir survived throughout a six-month follow-up period, provided they survived the first 48 h of therapy. Similarly, in a randomized study conducted by Anwer *et al.* [49], the overall survival rate among 16 cats diagnosed with effusive FIP was 87.5 %, while survival reached 100 % among cats that survived the initial 48 h of treatment. In light of these findings, the single-dose ozonated saline administration, given in addition to the conventional supportive treatments in our study, may have contributed to the prolonged survival of cats that survived the first 48 hours of therapy and the observed 100% survival rate throughout the follow-up period; this suggests that ozone administration could be considered a supportive (adjuvant) approach in the management of FIP. According to Roy *et al.* [45], of 11 cats in which GS-441524 treatment was unsuccessful, 8 achieved remission after switching to Molnupiravir [45]. This finding suggests that Molnupiravir may serve as a potentially effective alternative therapy in FIP cases that do not respond to GS-441524.

Ritz *et al.* [50] reported a mean survival time of 9 days in FIP-affected cats treated with feline interferon-omega. Similarly, Fischer *et al.* [51] documented an average survival time of 8 days in cats treated with polyprenyl immunostimulant. Tsai *et al.* [11] reported a mean survival time of 21.3 ± 19.9 d in cats diagnosed with effusive FIP. Collectively, these findings indicate that conventional and supportive treatment protocols are insufficient to substantially alter the fatal course of FIP.

Corticosteroids remain widely used in clinical practice as part of supportive therapy. In the study conducted by Moyadee *et al.* [12], cats with FIP receiving supportive treatment with prednisolone (Prednol®) exhibited a mean survival time of 38 d. This observation suggests that prednisolone may contribute to suppression of the inflammatory response and temporary alleviation of clinical signs; however, it does not represent a curative treatment when used alone. Similar to its role in the management of COVID-19, corticosteroids in FIP appear to function primarily as supportive agents rather than definitive therapeutic interventions. The primary therapeutic goal in FIP management is to control the excessive inflammatory response associated with disease progression while supporting the overall health status of the affected cats. In this context, supportive care strategies—including immune support, clinical symptom management, and stress reduction—represent essential components of the treatment protocol [9 , 30 , 52].

In the present study, the clinical and biochemical effects of ozonated saline solution as a supportive therapy were evaluated in cats diagnosed with FIP. All patients received conventional supportive treatment supplemented solely with ozonated saline. Following ozone therapy, increased appetite, normalization of mild pyrexia, improvement in mucosal coloration, and a marked enhancement in general clinical condition were observed. The achievement of a 100 % survival rate throughout the follow-up period, together with a marked reduction in clinical signs, suggests that ozonated saline administration may provide potential biological benefits as a supportive (adjuvant) approach in cats with FIP rather than exerting a direct curative effect. However, these findings do not constitute definitive evidence of therapeutic efficacy and should be interpreted as indicating possible favorable biological effects on clinical condition and oxidative stress parameters.

Data obtained in this study demonstrated that ozonated saline administration increased total antioxidant capacity and reduced oxidative stress levels within the first hour of treatment. Furthermore, an increase in native thiol levels accompanied by a decrease in disulfide levels indicated a strengthening of the

antioxidant defense system and a shift of the thiol–disulfide balance toward an antioxidant-favorable state. These findings suggest that ozone therapy may exert a protective role through modulation of oxidative stress and inflammatory processes.

CONCLUSION

This study provides pioneering and valuable evidence regarding the clinical and biochemical effects of ozonized saline solution administered in addition to standard supportive treatments in FIP cases. Following treatment, notable clinical improvements were observed in cats, including increased appetite, normalization of mild fever, enhanced activity levels, and improvement in mucosal coloration.

Effusion-related symptoms decreased, and respiratory distress showed significant alleviation. Moreover, ozonized saline treatment enhanced antioxidant capacity in the short term, reducing oxidative stress and positively modulating the thiol–disulfide balance. However, the chronic and progressive nature of FIP limited the long-term preservation of these beneficial effects.

One of the most notable findings of this study was that all cats receiving ozonated saline in addition to standard supportive therapy survived throughout the six-month follow-up period, as documented by clinical evaluations conducted at the first, third, and sixth months. Given the aggressive and frequently fatal course of FIP, this finding does not imply a direct curative effect of ozone therapy; rather, it suggests that ozonated saline may confer potential biological benefits when applied as a supportive (adjuvant) intervention.

However, the present results do not provide conclusive evidence of therapeutic efficacy and should be interpreted as indicating possible supportive effects on clinical status and oxidative stress–related parameters. Accordingly, further well-designed, controlled studies with larger sample sizes and extended follow-up durations are warranted to confirm these findings, clarify the role of ozone therapy in FIP management, and assess its reliability in clinical practice.

Conflict of Interest

The authors declare that they have no conflict of interest.

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