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The effects of combination of antibiotic and antioxidants on haemato-biochemical parameters in dogs affected with gastroenteritis

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Abstract
Gastroenteritis is one of the most prevalent problems in canine animal practice. In majority of the cases exact cause remain unclear so for treating such conditions symptomatic and supportive treatment plays vital role in therapy. Antioxidants have crucial role in the recovery of any disease condition, so keeping in mind these things present study was planned to see the effectiveness of incorporation of antioxidants in treatment regimen. For the study three different treatment trials were conducted with six dogs in each treatment group. All the dogs were treated with ceftriaxone-tazobactam along with antioxidants i.e. vitamin C and N-acetylcysteine in different combinations to assess their comparative effect on treatments. Haematological and biochemical parameters of affected dogs were compared with six healthy dogs on day 0, 3 and 5 of treatment trial. The gastroenteritis dogs showed haemo-concentration with increased packed cell volume, leukocytosis, neutrophilia with thrombocytopenia. Elevated liver and kidney function parameters along with decreased serum electrolytes were observed in all gastroenteritis dogs. The results of the study inferred that among all the three groups, group which was administered with both the antioxidants along with antibiotic showed better recovery than rest of the two groups.

Keywords: Gastroenteritis, ceftriaxone-tazobactam, antioxidants, vitamin C and N-acetylcysteine

1. Introduction
Gastroenteritis is characterized by different clinical signs such as diarrhoea, vomition, inappetence, lethargy, anaemia and dehydration (Banja *et al*., 2002) [2]. Diarrhoea and vomition associated with gastroenteritis is considered as an emergency in small animal practice because it is responsible for many deaths, particularly in young pups below six months of age. The precise etiologies of gastroenteritis remain unclear in many occasions, and sometimes overlapping (Juckett and Trivedi, 2011) [15]. Some studies have even revealed its association more often with lifestyle factors than specific pathogens (Stavisky *et al*., 2011) [19]. From past few years, oxidative stress has been paid much attention due to its important role in the pathogenesis of different diseases. Reactive Oxygen species (ROS) can be scavenged by antioxidant system which includes antioxidant enzymes like glutathione peroxidase, catalase and superoxide dismutase and non-enzymatic components involving vitamin E, vitamin C, vitamin A and selenium (Ighodaro and Akinloye, 2018) [13]. Vitamin C acts as cellular antioxidant vitamins which are present in the cell membrane and plasma lipoproteins. N-acetylcysteine (NAC), the body's primary cellular antioxidant, is a precursor to glutathione and its role in glutathione maintenance and metabolism is well established (Kelly, 1998) [16]. Gaykwad *et al.* (2016) [10] also observed that antioxidants like NAC are a potential additional treatment option that can be considered in canine parvovirus diarrhoea. Gastroenteritis may influence oxidative indices and such conditions may be targeted with supportive antioxidant therapy. That's why treatment must be oriented with antioxidant therapy to facilitate early and better recovery.

2. Materials and methods
Eighteen dogs which were reported to Veterinary Clinical Complex, LUVAS, Hisar with clinical signs of gastroenteritis such as vomiting, diarrhoea or haemorrhagic diarrhoea, lethargy, dehydration and depression included in the study. Group G1 constituted six apparently healthy dogs which were taken as control dogs. These affected dogs were randomly

divided into three different treatment groups G2, G3 and G4. Affected dogs in G2 group were administered with ceftriaxone-tazobactam and vitamin C while G3 dogs were administered with ceftriaxone-tazobactam alone. Group G4 dogs were administered with both the antioxidants vitamin C and N-acetylcysteine along with antibiotic. The antibiotic ceftriaxone-tazobactam was administered at the dosage of 25 mg/kg b.wt. i.m. o.d. The antioxidant therapy included Vitamin C @20 mg/kg b.wt. i.v. o.d. and N-acetylcysteine (NAC) @70 mg/kg b.wt. i.v. o.d. The supportive and symptomatic treatment in different groups included the administration of intravenous fluid Ringer's Lactate (RL), Normal Saline Solution (NSS) or Dextrose Normal Saline (DNS) on the basis of dehydration status and the clinical condition, antacids (pantoprazole @1 mg/kg i.v.), antiemetic (prochlorperazine @0.2 mg/kg b.wt. i.m.), antihistaminic (pheniramine maleate @0.5 mg/kg b.wt. i.m.), antipyretic (analgin @25 mg/kg b.wt. i.m.), vitamin B complex, amino acid preparation, antifibrinolytic agents (Tranexamic acid @10 mg/kg b.wt.) were administered as per the clinical condition of the animal. The blood samples collected in tubes coated with K_3EDTA were analyzed in automated hematology cell counter (MS4s, Melet Schlosing Lab.). The erythrocytic indices measured were haemoglobin (Hb) g/dl, packed cell volume (PCV) per cent. The leucocytic indices measured were total leucocyte count (TLC) m/mm^3 and differential leucocyte count (DLC) (per cent) comprising of neutrophils (N) per cent, lymphocytes (L) per cent, monocytes (M) per cent, eosinophils (E) per cent and basophils (B) per cent were also measured. The thrombocytic indices measured included was total thrombocyte count (THR) m/mm^3. The serum samples were analyzed using automated random access clinical chemistry analyzer (EM Destiny 180, Erba Diagnostics Mannheim GmbH). The liver function parameters measured were alanine amino transferase (ALT) (U/L), aspartate amino transferase (AST) (U/L) and total protein (g/dl). The kidney function parameters measured in serum were urea (mg/dl) and creatinine (mg/dl). Serum electrolytes were measured in EasyLyte EXPAND analyzer and included sodium (mEq/L), potassium (mEq/L) and chloride (mEq/L). Therapeutic evaluation was done on the basis of remission of clinical signs and normalization of haemato-biochemical values. The blood and serum parameters were analyzed on day 0 (pre-treatment), day 3 and day 5 of therapy (post-treatment). The data obtained was analyzed by applying suitable statistical methods using statistical software package (SPSS 16). For analysis of various haemato-biochemical parameters observed in affected dogs as compared with the healthy control dogs, the independent t-test was applied. For analysis of various haemato-biochemical parameters observed for therapeutic efficacy, within and between the groups, two-way analysis of variance (ANOVA) with repeated measures was applied. The results are presented as Mean ± S.E. at 5 per cent level of significance (P<0.05).

3. Results and discussion

Alterations in hematological parameters (Mean ± S.E.) of gastroenteritis dogs in different therapeutic groups are depicted in Table 1. In the present study, dogs affected with gastroenteritis (n=18) showed non-significant higher values of haemoglobin than the control group on day 0. Increased levels of haemoglobin were reported in various studies on gastroenteritis (Weiss and Tvedten, 2004 and Gaykwad *et al*., 2016) [21, 10] which might be due to excessive fluid loss resulting in dehydration. A non-significant decrease (P<0.05) in mean values of hemoglobin was observed from day 0 to day 5 of therapy in all the treatment groups as compared to the control group. Dogs in various therapeutic groups (n=18) were found to have a significant high mean values of PCV before the start of the treatment. Increased PCV levels observed might be due to severe dehydration and fluid losses through vomition and diarrhoea as also reported by Biswas *et al*. (2005) [7] and Bhargavi *et al*. (2017) [4]. The non-significant decreased level of haemoglobin and packed cell volume after treatment of five days might be attributed to the intravenous fluid administration in dehydrated dogs. Dogs in various therapeutic groups had non-significantly higher mean values of TLC on day 0 as compared to the healthy control group. Leukocytosis during gastroenteritis observed in the present study could be due to secondary bacterial invasion in the damaged intestinal epithelium as also reported by Bhargavi *et al*. (2017) [4] and Bishnoi *et al*. (2016) [6]. Dogs in the therapeutic groups showed normal values range of mean leucocyte count after five days of therapy. Non-significant higher (P<0.05) mean values of neutrophils were also observed in the dogs of all the treatment groups as compared to the control group on day 0. Neutrophilia in this study might be associated with secondary bacterial complications as also observed by Agnihotri *et al*. (2017) [1] and Bhargavi *et al*. (2017) [4]. On the contrary, Greene and Decaro (2012) [11] reported neutropenia in canine viral gastroenteritis which could be due to the destruction of mitotically active precursors of circulating leucocytes by CPV. Dogs in the therapeutic groups as well as dogs found positive or negative for CPV infection showed non-significant decrease in neutrophil count after treatment. However, group G4 which was administered with ceftriaxone-tazobactam along with both antioxidants (vitamin C and N-acetylcysteine) showed significant reduction in neutrophil count which is suggestive of good response to combined antioxidant therapy. Dogs in various therapeutic groups also showed a non-significant decrease in the mean lymphocyte count before the start of therapy as compared to the healthy control group of dogs. Changes in lymphocytic indices are relative to the neutrophil count observed. The lower levels of mean lymphocyte count might be due to the virus replication in the lymphoid organs resulting in lymphocytolysis as reported by Biswas *et al*. (2005) [7] and Dash *et al*. (2017) [9]. The changes in lymphocyte, monocyte and eosinophil count were found non-significant after treatment and were found to be in normal limits as a result of therapy. In the present study therapeutic groups showed non-significant lower mean values of thrombocyte count than healthy control group at day 0 before the start of therapy. Thrombocytopenia observed in the present study might be attributed to the decreased thrombocyte production or as a result of direct action of causative agents and immunologic components on thrombocytes or endothelium as suggested in similar studies by Bhargavi *et al*. (2017) [4]. Mean values of total platelet count was found to be increased non-significantly (P< 0.05) within all the groups from day 0 to day 5 of treatment.

Table 1: Alterations in hematological parameters (Mean ± S.E.) of gastroenteritis dogs in different therapeutic groups

Parameters	Day	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Hemoglobin (g/dl)	0	10.67±0.69	11.23±0.85	12.05±0.90	13.48±0.79
	3	10.67±0.69	11.20±1.00	11.23±1.01	12.88±1.46
	5	10.67±0.69	11.17±0.91	11.06±1.49	11.73±1.74
PCV (%)	0	34.83±2.71	37.18±2.94	40.08±3.41	40.88±2.75
	3	34.83±2.71	36.63±2.86	39.43±3.57	38.00±4.06
	5	34.83±2.71	35.28±3.05	37.70±5.54	36.13±4.69
TLC (m/mm^3)	0	13.02±0.54	16.79±3.33	16.33±3.22	13.26±355
	3	13.02±0.54	15.16±4.10	15.15±2.82	13.48±2.45
	5	13.02±0.54	12.62±2.08	13.03±1.26	12.54±5.67
Neutrophil (%)	0	72.17±2.95	79.50±4.05	73.20±6.78	$89.50±1.75^b$
	3	72.17±2.95	77.83±2.54	72.50±7.04	$83.20±2.44^a$
	5	72.17±2.95	77.33±3.17	77.50±3.18	$80.60±0.73^a$
Lymphocyte (%)	0	23.17±3.71	18.00±3.74	22.20±6.00	$8.00±0.93^a$
	3	23.17±3.71	19.67±2.76	21.00±6.25	$12.00±0.71^b$
	5	23.17±3.71	21.17±2.89	19.50±4.51	$16.67±0.95^c$
Monocyte (%)	0	3.50±0.62	1.00±0.26	2.20±0.70	3.00±1.15
	3	3.50±0.62	0.83±0.31	3.33±1.35	4.40±1.60
	5	3.50±0.62	1.50±0.72	3.00±1.50	3.00±0.82
Eosinophil (%)	0	1.17±0.54	1.50±0.50	2.40±1.13	0.33±0.33
	3	1.17±0.54	1.67±0.61	4.00±2.73	0.40±0.40
	5	1.17±0.54	0.00±0.00	0.00±0.00	0.33±0.33
Thrombocyte (m/mm^3)	0	418.00±59.03	259.17±69.07	256.50±67.57	285.17±64.35
	3	418.00±59.03	307.50±80.68	350.00±105.70	378.20±112.32
	5	418.00±59.03	331.50±68.10	437.00±48.59	388.67±77.11

The means bearing different superscripts (a, b and c) differ significantly ($P<0.05$) within the groups.

Biochemical alterations (Mean ± S.E.) in gastroenteritis dogs in different therapeutic groups are depicted in Table 2. Gastroenteritis dogs in various therapeutic groups G2 and G4 showed non-significant ($P<0.05$) higher values of ALT as compared to the healthy control group before the start of treatment on day 0. Non-significant higher values of AST were observed in groups G2, G3 and G4 than control group on day 0. These elevated levels of liver function parameters could be due to reactive hepatopathy as also observed by Berghoff and Steiner (2011) [3]. Increase in ALT may occur as a result of hepatic hypoxia secondary to severe hypovolemia or the absorption of toxic substances due to loss of the gut barrier (Shah *et al*., 2013) [18]. Dogs in the therapeutic groups G2 and G3 showed higher levels of mean total protein as compared to control group at the start of treatment while dogs in the group G4 showed lower values than the healthy control group. The decrease in the levels of total protein might be due to anorexia and decreased absorption through villi of intestines. Similar findings were also reported by Sagar *et al*. (2008) [17] and Bhargavi *et al*. (2017) [4]. While, non-significant higher values of total protein was observed by Surendhar *et al*. (2018) [20] which could be because of dehydration caused by diarrhea losses. In the dogs belonging to various therapeutic groups, the mean values of BUN and serum creatinine were also observed to be higher than the healthy control group of dogs before the start of therapy. The increased values of BUN are suggestive of pre renal azotemia which might be because of reduced glomerular filtration rate (Bhat *et al*., 2015) [5]. Mean values of electrolyte parameters i.e. sodium, potassium and chloride were non-significantly found low in various therapeutic groups as compared to the healthy control group on day 0. Hypokalemia was also reported by Bhargavi *et al*. (2017) [4] in diarrhea dogs which might be due to the loss of potassium in severe vomition and diarrhoea. Haligur *et al*. (2009) [12] and Joshi *et al*. (2012) [14] also suggested that severe vomition, diarrhoea and dehydration in the dogs affected with gastroenteritis of varied etiologies might be responsible for hyponatremia. Hypochloremia might be due to the loss of chloride ions through vomition and diarrhoea and resulting intestinal villous atrophy, which is in agreement with Burchell *et al*. (2014) [4]. All the biochemical parameters were restored after five days of therapy.

The therapeutic management was based mainly on supportive care for the correction of electrolyte and fluid imbalance and to prevent secondary bacterial infections. Best management strategy requires aggressive treatment with fluid therapy, correction of hypoglycemia and any electrolyte disturbances. Antibiotic treatment with ceftriaxone-tazobactam proved to be effective in clinical recovery against canine parvoviral gastroenteritis (Bhargavi *et al*., 2017 and Dash *et al*., 2017) [4, 9]. Ceftriaxone, a third generation cephalosporin has broad spectrum of activity against few gram-positive and most of the gram-negative bacteria and used primarily to treat serious infections, particularly against susceptible *Enterobacteriaceae* those do not respond to other drugs (Sandhu, 2013) [18].

Table 2: Biochemical alterations (Mean ± S.E.) in gastroenteritis dogs in different therapeutic groups

Parameters	Day	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
ALT (IU/L)	0	29.95±2.59	61.63±20.03	26.45±2.91	31.94±1.89
	3	29.95±2.59	44.13±11.52	21.08±1.21	28.57±3.26
	5	29.95±2.59	41.88±6.8	17.98±1.51	30.13±5.37
AST (IU/L)	0	39.27±3.74	49.14±6.69	40.60±4.82	40.05±6.54
	3	39.27±3.74	42.46±5.76	37.20±6.36	34.72±5.42
	5	39.27±3.74	37.56±3.32	34.62±4.27	26.67±2.48
Total Protein	0	6.38±0.29	6.52±0.79	6.98±1.13	6.07±1.37

(g/dl)	3	6.38±0.29	6.10±0.59	5.48±0.92	5.38±0.89
	5	6.38±0.29	5.52±0.37	4.68±0.77	4.96±1.06
BUN (mg/dl)	0	20.72±2.17	34.65±7.65	85.00±34.29	64.87±28.75
	3	20.72±2.17	29.95±6.62	69.62±23.27	54.87±25.50
	5	20.72±2.17	26.44±5.17	67.53±19.77	47.68±23.94
Creatinine (mg/dl)	0	0.82±0.09	0.84±0.14	2.20±0.89	1.67±0.57
	3	0.82±0.09	0.88±0.10	1.73±0.51	1.38±0.36
	5	0.82±0.09	0.93±0.05	1.73±0.47	1.15±0.15
Sodium (mEq/L)	0	143.15±2.10	131.70±6.26	137.50±2.87	137.70±3.01
	3	143.15±2.10	130.45±8.07	139.72±2.13	137.77±2.61
	5	143.15±2.10	141.10±5.30	140.63±1.47	133.98±4.50
Potassium (mEq/L)	0	5.20±0.22	3.89±0.14	4.16±0.35	4.23±0.66
	3	5.20±0.22	4.26±0.30	4.21±0.22	4.73±0.53
	5	5.20±0.22	4.76±0.53	4.64±0.17	4.88±0.47
Chloride (mEq/L)	0	107.80±1.05	99.03±5.73	101.72±4.57	103.52±3.37
	3	107.80±1.05	99.30±7.66	106.66±3.60	107.48±2.50
	5	107.80±1.05	105.24±5.16	108.28±3.47	107.62±3.27

4. Conclusion

The present study concluded that use of antioxidants vitamin C and N-acetylcysteine with antibiotics ceftriaxone-tazobactam resulted in early clinical recovery and restoration of haematological and biochemical parameters in five days which may suggest that administration of antibiotics with adjunct antioxidant therapy leads to better and effective recovery in gastroenteritis dogs.

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