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Study on effect of ranitidine along with N-acetylcysteine in canine gastritis

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Abstract
The study was conducted for comparative assessment of Clinical-haemato-biochemical parameters and comparative therapeutic evaluation of the efficacy of H2- blocker (Ranitidine) along with N-Acetylcysteine in clinical cases of Canine Gastritis. Six healthy and twelve gastritis affected dogs were selected for the study based on clinical observations, Haemato-biochemical parameters. The Haemato-biochemical alterations included increased haematocrit, PCV, TLC, Neutrophil, Monocytes, and Eosinophils, and an increase in serum Histamine levels in gastritis affected dogs. On comparative evaluation, H2- blocker (Ranitidine) along with N-Acetylcysteine treated group showed significant (P<0.05) changes in Haemato-biochemical parameters on day 5 of therapy as compared to Ranitidine treated groups.

Keywords: N-acetylcysteine, ranitidine, histamine, gastrin, gastritis

1. Introduction
The concept of "Gastritis" as the inflammation of the inner lining of the stomach was first given by German physician, Georg Ernst Stahl in 1728 (quoted by Bock, 1974) [1]. The gastritis is an inflammatory condition of the gastric mucosa which is characterized by the existence of elementary histological alternations. (Rugge *et al.*, 2003) [2].

In gastritis the inflammatory components (e.g., endothelial cells, neutrophils, and mast cells) become activated and there is the release of inflammatory cell mediators (e.g. histamine, leukotrienes, platelet-activating factor, proteolytic enzymes, and free radicals). Histamine promotes gastric acid secretion, whereas other mediators promote vascular changes (e.g., vasodilation, vasoconstriction, increased capillary permeability) leads to Edema and translocation of inflammatory cells that plugged the capillary lumen. These are intensifying to the initial gastric mucosal injury by reducing blood flow, leads to ischemia, disturbed epithelial cell layer restoration, and reduced secretion of mucus and PG-E (Sorjonen *et al.*, 1983; Guilford *et al.*, 1996) [3, 4].

It is difficult to prevent the generation of ROS but the proper strategies prevent the gastric mucosal damage and fastening of recovery from oxidative stress (Aditi *et al.*, 2012) [5].

N-acetylcysteine (NAC) produces a significant gastro protection, similar to that observed in ranitidine (reference drug), indicating the role of NAC protective mechanisms in providing reduced glutathione (GSH) as an endogenous antioxidant to protect the gastric mucosa through its function as a scavenger of free radical, which protect thiol groups from oxidation (Rushworth and Megson, 2014: Tanaka and Yuda, 1996) [6, 7].

2. Material and Method
2.1 Selection of dogs
The clinical cases presented to the TVCC, IVRI, Izatnagar; Bareilly (U.P.) with symptoms suggestive of Gastritis were acts as a subject for this study. Consent of the owner was obtained before inclusion of any clinical cases in this study. Information on the health status of the animals was obtained by physical examination and a questionnaire. Besides a thorough clinical examination of the dogs for the following laboratory parameters were examined.

Dogs of any age, sex or weight were accepted in the trial. A full clinical and drug history was obtained. The duration of clinical signs before admission, treatments administered prior to admission and any previous history recorded.

2.2 Questionnaire

Case no: Breed: Age: Sex:

Weight:

Owner's name:

Address:

1. Frequency of feeding?
2. Type of food?

a) Commercial b) homemade c) both

3. Deworming status? Yes / No
4. Vaccination status? Yes / No
5. History of any illness or surgical operation? Yes / No
6. History of any NSAIDS/corticosteroid administration? Yes/ No
7. Licking of cold water? Yes/ No
8. Hyper salivation? Yes/ No
9. Pain on palpation of stomach? Yes/ No
10. History of ingestion of foreign objects? Yes/ No
11. Onset of vomiting?

a) Immediately after feeding b) after half to one hour of feeding c) no appropriate pattern

12. Frequency of vomiting?

a) 2 times b) 2 to 5 times c) > 5 times

13. Colour of vomitus?
14. Inappetence? Yes/ No
15. Diarrhoea/constipation/melena?

2.3. Experiment design

Our study was consisting of 18 dogs. The important clinical parameters of all the selected animals i.e., status of appetite (anorexia / inappetence), frequency and content of vomiting and melena were recorded on the day of presentation (day 0), 3 days and day 5 of therapeutic study. All the dogs were divided into 3 groups *viz*. T0 (Control), T1, and T2 (Treatment), and each group was consisted of 6 dogs, the first group was taken as Control (T0) and other groups (diseased dogs) were used for therapeutic studies. All the diseased dogs were treated with the same antibiotic, antiemetic and fluid therapy. T1 group was treated with Ranitidine 1mg/ kg BW IV TID and T2 group was treated with Ranitidine 1mg/ kg BW IV TID and N- Acetylcysteine @ 70 mg/ kg BW IV OD. All therapy was given for 5 days and may be extended for 2-5 days more if required.

3. Sample Collection

Whole blood was collected aseptically from a saphenous/cephalic vein in EDTA vials and clot activating vials from all the selected dogs for the estimation of haematological parameters. For serum biochemistry, blood was subjected to centrifugation at 3000 rpm for 10 minutes. Collected serum samples were preserved at -20 ºC for subsequent analysis.

3.1. Laboratory Analysis

3.2. Haemato-biochemical parameters

For hematological parameters, 3ml blood was collected aseptically from the saphenous/ cephalic vein of each dog in EDTA vials. Samples were taken on the day 0, day 3 and day 5. The following parameters were studied as per standard techniques:

a) Estimation of hemoglobin concentration (Hb): Expressed in g/dl.
b) Total Erythrocyte Count (TEC): Expressed in million per microliter (µl) of blood.
c) Packed Cell Volume (PCV): Expressed in%.
d) Total Leukocyte Count (TLC): Expressed as thousand/mm3.
e) Blood smear examination for DLC: Expressed in percentage.

3.3. Biochemical parameter

A) Histamine

Estimation was using the Canine Histamine ELISA kits and results were expressed as ng/ ml.

4. Results and Discussion

Table 1: Clinical observations of Healthy Control dogs in Group 1 (Healthy Control- placebo treated)

Animal no.	Days	Clinical signs and symptoms				
		Inappetence/Anorexia	Vomiting			Melena
			Gastric contents with blood	Gastric contents with bile	Gastric contents	
1	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
2	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
3	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
4	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
5	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
6	Day 0	-	-	-	-	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-

Table 2: Clinical observations of dogs with gastritis in Group II (Treatment 1 – Ranitidine treated)

Animal no.	Days	Clinical signs and symptoms				
		Inappetence/Anorexia	Vomiting			Melena
			Gastric contents with blood	Gastric contents with bile	Gastric contents	
1	Day 0	Present	Present	-	-	-
	Day 3	Present	-	-	Present	-
	Day 5	-	-	-	-	-
2	Day 0	Present	-	-	Present	Present
	Day 3	Present	-	-	-	-
	Day 5	-	-	-	-	-
3	Day 0	Present	-	-	Present	Present
	Day 3	-	-	-	Present	-
	Day 5	-	-	-	-	-
4	Day 0	Present	Present	-	Present	-
	Day 3	Present	-	-	Present	-
	Day 5	-	-	-	-	-
5	Day 0	Present	-	-	Present	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
6	Day 0	Present	-	Present	Present	-
	Day 3	Present	-	-	-	-
	Day 5	-	-	-	-	-

Table 3: Clinical observations of dogs with gastritis in Group III (Treatment 2 - Ranitidine + N-Acetylcysteine treated)

Animal no.	Days	Clinical signs and symptoms				
		Inappetence/Anorexia	Vomiting			Melena
			Gastric contents with blood	Gastric contents with bile	Gastric contents	
1	Day 0	Present	-	-	Present	Present
	Day 3	Present	-	-	-	-
	Day 5	-	-	-	-	-
2	Day 0	Present	Present	-	Present	-
	Day 3	Present	-	-	-	-
	Day 5	-	-	-	-	-
3	Day 0	Present	Present	-	Present	Present
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
4	Day 0	Present	-	-	Present	-
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-
5	Day 0	Present	Present	-	Present	Present
	Day 3	Present	-	-	Present	-

	Day 5	-	-	-	-	-
6	Day 0	Present	-	-	Present	Present
	Day 3	-	-	-	-	-
	Day 5	-	-	-	-	-

4.1. Laboratory Analysis

4.1.1. Hematological parameters

Mean±SE values of various haematological parameters of Group I (healthy control), Group II (T1-Ranitidine), Group III (T4- Ranitidine + N-Acetylcysteine treated), dogs on day of presentation (0th day), day 3 and day 5 of therapy are shown in table 4.

In Group I (Healthy control) dogs, haemoglobin level (Mean±SE) was 11.68±0.22aB g/dl on day of presentation while on day 3 and day 5 of therapy haemoglobin levels (Mean±SE) were 11.91±0.24aB g/dl and 12.19±0.21aA g/dl respectively. The Mean±SE value of PCV was 36.39±0.25aD% on the day of presentation while on day 3 and day 5 of therapy PCV values were 35.78±0.21aC% and 35.98±0.18aB% respectively. The Mean±SE value of TEC was 5.23±0.08aB ×106/µl on day of presentation while on day 3 and day 5 of therapy TEC values were 5.29±0.07aB ×106/µl and 5.14±0.14aA ×106/µl respectively. The Mean±SE value of TLC was 9.38±0.38aB ×103/µl on day of presentation while on day 3 and day 5 of therapy TLC values were 8.74±0.31aC ×103/µl and 8.49±0.19aD ×103/µl respectively. The Neutrophils values (Mean±SE) on day of presentation, day 3 and day 5 of therapy were 71.17±1.19aA%, 71.67±0.88aA%, and 69.17±0.87aA% respectively. The Mean±SE values of Lymphocytes on day of presentation, day 3 and day 5 of therapy were27.00±1.06aA%, 26.17±1.28aA% and 27.00±1.06aA% respectively. The Mean±SE values of Monocytes on day of presentation, day 3 and day 5 of therapy were 1.17±0.31aA%, 0.83±0.17aA%, and 1.00±0.37aA% respectively. The Mean±SE values of Eosinophils on day of presentation, day 3 and day 5 of therapy were 0.83±0.31aA%, 0.67±0.33aA%, and 1.33±0.42aA% respectively. The Mean±SE values of Basophils on day of presentation, day 3 and day 5 of therapy were 0.00±0.00aA%, 00.17±0.17aA%, and 0.17±0.17aA% respectively.

In Group II (T1= Ranitidine treated) dogs, haemoglobin level Mean±SE was 15.31±0.54aA g/dl while on day 3 and day 5 of therapy Hb levels were 13.37±0.43bAB g/dl and 11.89±0.28bABC g/dl respectively. The Mean±SE value of PCV was 41.44±0.61aBC% on day presentation while on day 3 and day 5 of therapy PCV values were 40.23±0.36abB% and 39.42±0.50bA% respectively. The Mean±SE TEC value was 5.94±0.25aAB ×106/µl on day of presentation while on day 3 and day 5 of therapy TEC values were 5.51±0.19abAB ×106/µl and 5.11±0.08bA ×106/µl respectively. The Mean±SE TLC value was 12.88±0.46aA ×103/µl on day of presentation while on day 3 and day 5 of therapy TLC values were 10.70±0.58bB ×103/µl and 10.53±0.35bcC ×103/µl respectively. The Mean±SE values of Neutrophils on day of presentation, day 3 and day 5 of therapy were 77.00±1.29aA, 75.67±1.82aA%, and 70.17±0.87bA% respectively. The Mean±SE values of Lymphocytes on day of presentation, day 3 and day 5 of therapy were 18.00±1.86aB%, 19.00±1.57aB%, and 19.83±1.17aB% respectively. The Mean±SE values of Monocytes on day of presentation, day 3 and day 5 of therapy were 0.67±0.21aA%, 0.83±0.17aA%, and 0.83±0.31aA%respectively. The Mean±SE values of Eosinophils on day of presentation, day 3 and day 5 of therapy were 0.83±0.48aA%, 0.50±0.34aA%and 0.67±0.33aA%respectively. No basophils were found in this group.

In Group III (Ranitidine + N-Acetylcysteine treated) dogs, haemoglobin level Mean±SE was 14.34±0.24aA g/dl while on day 3 and day 5 of therapy Hb levels were 13.08±0.38bAB g/dl and 12.40±0.22bcABC g/dl respectively. The Mean±SE value of PCV was 42.57±0.45aBC% on day presentation while on day 3 and day 5 of therapy PCV values were 41.02±0.31bAB% and 39.71±0.32bA% respectively. The Mean±SE TEC value was 6.34±0.23aA ×106/µl on day of presentation while on day 3 and day 5 of therapy TEC values were 5.54±0.19bAB ×106/µl and 5.10±0.11bcA /µl respectively. The Mean±SE TLC value was 14.35±0.48aA ×103/µl on day of presentation while on day 3 and day 5 of therapy TLC values were 12.90±0.32bA ×103/µl and 12.90±0.32bA ×103/µl respectively. The Mean±SE values of Neutrophils on day of presentation, day 3 and day 5 of therapy were 77.17±2.18aA%, 69.83±1.33bA%, and 68.83±1.40bcA% respectively. The Mean±SE values of Lymphocytes on day of presentation, day 3 and day 5 of therapy were 18.83±1.54aB%, 21.83±1.35bAB%, and 23.33±1.86bcAB% respectively. The Mean±SE values of Monocytes on day of presentation, day 3 and day 5 of therapy were 1.00±0.26aA%, 1.00±0.37aA%, and 1.50±0.43aA%respectively. The Mean±SE values of Eosinophils on day of presentation, day 3 and day 5 of therapy were 0.67±0.21aA%, 0.83±0.31aA%, and 1.17±0.31aA% respectively. No Basophils were seen in this Group.

Table 4: Mean±SE values of haematological observations of Group I, Group II, Group III, animals (n= 6 in each group)

Haematological Parameters	Day 0	Day 3	Day 5
Haemoglobin (g/dl)			
Group –I (Healthy Control)	$11.68±0.22^{aB}$	$11.91±0.24^{aB}$	$12.19±0.21^{aA}$
Group-II(T1)	$15.31±0.54^{aA}$	$13.37±0.43^{bAB}$	$11.89±0.28^{bABC}$
Group-III (T2)	$14.34±0.24^{aA}$	$13.08±0.38^{bAB}$	$12.40±0.22^{bABC}$
TEC (×10^6/µl)			
Group –I (Healthy Control)	$5.23±0.08^{aB}$	$5.29±0.07^{aB}$	$5.14±0.14^{aA}$
Group-II(T1)	$5.94±0.25^{aAB}$	$5.51±0.19^{abAB}$	$5.11±0.08^{bA}$
Group-III (T2)	$6.34±0.23^{aA}$	$5.54±0.19^{bAB}$	$5.10±0.11^{bcA}$
PCV (%)			
Group –I (Healthy Control)	$36.39±0.25^{aD}$	$35.78±0.21^{aC}$	$35.98±0.18^{aB}$
Group-II(T1)	$41.44±0.61^{aBC}$	$40.23±0.36^{abB}$	$39.42±0.50^{bA}$
Group-III (T2)	$42.57±0.45^{aBC}$	$41.02±0.31^{bAB}$	$39.71±0.32^{bA}$
TLC (×10^3/µl)			

Group –I (Healthy Control)	9.38±0.38^{aB}	8.74±0.31^{aC}	8.49±0.19^{aD}
Group-II(T1)	12.88±0.46^{aA}	10.70±0.58^{bB}	10.53±0.35^{bcC}
Group-III (T2)	14.35±0.48^{aA}	12.90±0.32^{bA}	12.53±0.26^{bcAB}
DLC			
Neutrophils (%)			
Group –I (Healthy Control)	71.17±1.19^{aA}	71.67±0.88^{aA}	69.17±0.87^{aA}
Group-II(T1)	77.00±1.29^{aA}	75.67±1.82^{aA}	70.17±0.87^{bA}
Group-III (T2)	77.17±2.18^{aA}	69.83±1.33^{bA}	68.83±1.40^{bcA}
Lymphocytes (%)			
Group –I (Healthy Control)	27.00±1.06^{aA}	26.17±1.28^{aA}	27.00±1.06^{aA}
Group-II(T1)	18.00±1.86^{aB}	19.00±1.57^{aB}	19.83±1.17^{aB}
Group-III (T2)	18.83±1.54^{aB}	21.83±1.35^{bAB}	23.33±1.86^{bcAB}
Monocytes (%)			
Group –I (Healthy Control)	1.17±0.31^{aA}	0.83±0.17^{aA}	1.00±0.37^{aA}
Group-II(T1)	0.67±0.21^{aA}	0.83±0.17^{aA}	0.83±0.31^{aA}
Group-III(T2)	1.00±0.26^{aA}	1.00±0.37^{aA}	1.50±0.43^{aA}
Eosinophils (%)			
Group –I (Healthy Control)	0.83±0.31^{aA}	0.67±0.33^{aA}	1.33±0.42^{aA}
Group-II(T1)	0.83±0.48^{aA}	0.50±0.34^{aA}	0.67±0.33^{aA}
Group-III (T2)	0.67±0.21^{aA}	0.83±0.31^{aA}	1.17±0.31^{aA}
Basophils (%)			
Group –I (Healthy Control)	0.00±0.00^{aA}	0.17±0.17^{aA}	0.17±0.17^{aA}
Group-II(T1)	0.00±0.00^{aA}	0.00±0.00^{aA}	0.00±0.00^{aA}
Group-III (T2)	0.00±0.00^{aA}	0.00±0.00^{aA}	0.00±0.00^{aA}

Superscript a, b, c, d depicts statistically significant (P<0.05) difference within the row

Superscript A, B, C, D depicts statistically significant (*P*<0.05) difference within the column

Letters connected by same alphabet are not statistically significant.

Comparative analysis of the study revealed that there are no much significant differences in the haematological values other than PCV between the treatment groups.

Haemoconcentration as a consequence of dehydration due to vomiting may occur in cases of gastritis (Webb and Twedt, 2003; Ettinger and Fieldman, 2005) [8, 9]. It also reported that haematocrit may decrease in association with severe gastric erosions and ulcer disease due to acute or chronic blood loss. Microcytic and hypochromic anaemia was reported in different studies (Harvey *et al.*, 2008) [10]. Stanton and Bright (1989) [11] and also there are some reports that there is a normal leukogram in dogs with gastric affections. However, marked neutrophilia with a left shift was recorded in 29 dogs affected with gastritis and 32 of 40 dogs had non-regenerative normocytic/normochromic anaemia. Anaemia (haematocrit <0•37) was found in 34 (41%) dogs with gastric mucosa lesions. Anaemia occurred more frequently in dogs with a long duration of clinical signs than dogs with short duration of signs (Fitzerald *et al.*, 2017) [12].

It has been reported that NAC stimulates pluripotent stem cells to differentiate toward hematopoietic cells in a laboratory animal model (Berniakovich *et al.*, 2012) [13]. However, there is a very scarce study which reflects the effects of Ranitidine on haematological parameters in canine gastritis.

4.1.2. Serum Biochemical Alteration (Histamine)

Mean±SE values of Histamine, Group I (healthy control), Group II (T1-Ranitidine), Group III (T2- Ranitidine + N-Acetylcysteine treated), dogs on day of presentation (0th day), day 3 and day 5 of therapy are shown in table 5.

Group II (T1-Ranitidine treated) dogs, On the day of presentation, Serum Histamine level was 6.13±0.10aC ng/ml while on day 3 and day 5 of therapy Serum Histamine levels were 5.12±0.14bA ng/ml and 3.18±0.05cC ng/ml respectively. The Serum Histamine value on day 3 and day 5 of therapy was significantly (*P* <0.05) lower than the day 0 value of serum Histamine. In Group III (T2-Ranitidine + N-Acetylcysteine treated) dogs, On the day of presentation, Serum Histamine level was 6.43±0.17aBC ng/ml while on day 3 and day 5 of therapy Serum Histamine levels were 4.53±0.11bBC ng/ml and 3.65±0.08cB ng/ml respectively. The Serum Histamine value on day 3 and day 5 of therapy was significantly (*P*<0.05) lower than the day 0 value of serum Histamine.

Table 5: Mean±SE values of biochemical observations of Group I, Group II, and Group III animals (n= 6 in each group)

Histamine (ng/ml)			
Group –I (Healthy Control)	1.05±0.09^{aD}	0.87±0.06^{aD}	0.67±0.05^{aF}
Group-II(T1)	6.13±0.10^{aC}	5.12±0.14^{bA}	3.18±0.05^{cC}
Group-III (T2)	6.43±0.17^{aBC}	4.53±0.11^{bBC}	3.65±0.08^{cB}

The physiological significance of histamine signalling mediated by H2-receptor in gastric acid secretion has been demonstrated by pharmacological studies using selective antagonists such as Ranitidine, which have a potent inhibitory effect on secretory response. In fact, these antagonists have been used clinically for the treatment of peptic ulcer (Feldman *et al.*, 1990) [14].

According to some reports NAC attenuates and reduces the inflammation through inhibiting variety of cytokines such as TNF-α, interferon-y, IL-8, and IL-6, and/or to restore the cellular redox status, and regulates the activity of redox-sensitive cell signalling pathways, such as NF-KB that control pro-inflammatory genes, indicating its protective action against cytokines-induced organ damage (Sadowska *et al.*, 2007; Lee *et al.*, 2013) [15, 16].

In light of these issues, studies gave evidence that both anti-oxidant and anti-inflammatory activities of NAC are the major properties that actively participate in the gastro protective activity (Matsuyama *et al.*, 2006) [17].

Evidence from a variety of pathological and toxicological studies, such as ischemia-reperfusion injury, chemically induced oxidative injury, radiation damage, aging, and

degenerative disease, specify that GSH is a major component of physiological systems protecting against oxidative and free radical-mediated cell injury (Shan *et al.*, 1990) [18]. In the presence of NAC, the ROS production and consequently oxidative stress were significantly decreased, as reported in many *in vitro* and *in vivo* studies (Gillissen & Nowak, 1998) [19].

In an *in vitro* model by Mann *et al.* to assess the gastro-protective effect of NAC, they found the healing of mucosal lesions that induced by HCl was promoted and hastened by low-dose of NAC (Mann *et al.*, 1992) [20].

6. Statistical analysis

The data generated from the experimental study were subjected to statistical analysis by following the standard procedures of Snedecor and Cochran (1994). Tukey's post hoc testing was used for calculating differences amongst different means. The statistical package used was SPSS 20.0 for analysis of data.

7. Conclusions

Keeping in view the importance of gastritis in canine, paucity of information on understanding of pathophysiology and diagnostic parameters, the present study was planned to study the effect of ranitidine along with N-Acetylcysteine in clinical cases of canine gastritis, and to conclude:

- Vomiting is the cardinal sign of gastritis in dogs.
- Serum Histamine levels can be used as a sensitive biomarker for serological diagnosis of gastric inflammation.
- Ranitidine along with N-Acetylcysteine can act as a potential therapeutic alternative in Veterinary Medicine due to healing rates are consistently higher, irrespective of baseline disease severity.

8. References

1. Bock OAA. The Relationship between Chronic Gastritis, Gastric Ulceration and Carcinoma of the Stomach. S. Afr. Med. J 1974;48:2063.
2. Rugge M, Russo VM, Guido M. What have we learnt from gastric biopsy? Alimentary pharmacology & therapeutics 2003;17:68-74.
3. Sorjonen DC, Dillon AR, Powers RD, Spano JS. Effects of dexamethasone and surgical hypotension on the stomach of dogs: clinical, endoscopic, and pathologic evaluations. Am. J Vet. Res 1983;44(7):1233-1237.
4. Guilford WG, Center SA, Strombeck DR, Williams DA, Meyer DJ. Strombeck's small animal gastroenterology (No. Ed. 3,). WB Saunders Co 1996.
5. Aditi A, Graham DY. Vitamin C, gastritis, and gastric disease: a historical review and update. Dig. Dis. Sci 2012;57(10):2504-2515.
6. Rushworth GF, Megson IL. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacology & therapeutics 2014;141(2):150-159.
7. Tanaka J, Yuda Y. Lipid peroxidation in gastric mucosal lesions induced by indomethacin in rat. Biological and Pharmaceutical Bulletin 1996;19(5):716-720.
8. Webb C, Twedt DC. Canine gastritis. Veterinary Clinics of North America: Small Anim. Pract 2003;33(5):969-985.
9. Ettinger SJ, Feldman EC. Textbook of veterinary internal medicine 2005.
10. Harvey JW. Iron metabolism and its disorders. Clinical biochemistry of domestic animals 2008, 259-286.
11. Stanton ME, Bright RM. Gastroduodenal ulceration in dogs. J Vet. Intern. Med 1989;3(4):238-244.
12. Fitzgerald E, Barfield D, Lee KCL, Lamb CR. Clinical findings and results of diagnostic imaging in 82 dogs with gastrointestinal ulceration. J Small. Anim. Pract 2017;58(4):211-218.
13. Berniakovich I, Laricchia-Robbio L, Belmonte JCI. N-acetylcysteine protects induced pluripotent stem cells from *in vitro* stress: impact on differentiation outcome. International Journal of Developmental Biology 2012;56(9):729-735.
14. Feldman M, Burton ME. Histamine 2-receptor antagonists. Standard therapy for acid-peptic diseases (2). N. Engl. J Med 1990;323:1749-1755.
15. Sadowska AM, Manuel-Y-Keenoy B, De Backer WA. Antioxidant and antiinflammatory efficacy of NAC in the treatment of COPD: discordant *in vitro* and *in vivo* dose-effects: a review. Pulmonary Pharmacology & Therapeutics 2007;20(1):9-22.
16. Lee JH, Jo YH, Kim K, Lee JH, Rim KP, Kwon WY *et al.* Effect of N-acetylcysteine (NAC) on acute lung injury and acute kidney injury in hemorrhagic shock. Resuscitation 2013;84(1):121-127.
17. Matsuyama T, Morita T, Horikiri Y, Yamahara H, Yoshino H. Improved nasal absorption of salmon calcitonin by powdery formulation with N-acetyl-L-cysteine as a mucolytic agent. Journal of controlled release 2006;115(2):183-188.
18. Shan X, Aw TY, Jones DP. Glutathione-dependent projection against oxidative injury. Pharmacology & therapeutics 1990;47(1):61-71.
19. Gillissen A, Nowak D. Characterization of N-acetylcysteine and ambroxol in anti-oxidant therapy. Respiratory medicine 1998;92(4):609-623.
20. Mann NS, Mann SK, Brawn PN, Weaver B. Effect of zinc sulfate and acetylcysteine on experimental gastric ulcer: *in vitro* study. Digestion 1992;53(1-2):108-113.
21. Snedecor GW, Cochran WG. Statistical methods, 8th Edn.Ames: Iowa State University. Press Iowa 1994.