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A study on serum gastrin-17 and cortisol levels in canine gastritis

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Abstract
The study was conducted on six clinically healthy dogs and twenty dogs showing symptoms of gastritis and divided into two groups i.e healthy control and diseased dogs to evaluate changes in clinico-biochemical parameters, Gastrin and Cortisol levels in clinical cases of gastritis. Blood sampling was done on the day of presentation in healthy control (Group I) and in diseased dogs (Group II). There was significant ($P<0.01$) fall in Gastrin-17 levels and rise in Cortisol levels in diseased group indicating role of gastrin and cortisol in pathophysiology of gastritis in dogs.

Keywords: Dogs, gastritis, gastrin, cortisol

Introduction
Gastritis is a common finding in dogs with 35 per cent of dogs investigated for chronic vomiting and 26-48 per cent of asymptomatic dogs affected. Despite the high prevalence of gastritis in dogs, an underlying cause is rarely identified (Wiinberg *et al*., 2005) [21]. Gastritis is inflammation of the stomach which is a frequently cited differential yet rarely characterized diagnosis in cases of canine anorexia and vomiting. Gastrins are physiologically produced primarily by antral G cells and endocrine cells of the gut. Serum gastrin has become an important biomarker for gastric antrum inflammation (Fourmy *et al*., 2011). Gastrin-17 is an essential hormone for the maintenance of normal gastric homeostasis and any disturbances in its secretion or processing caused by diseases must be taken into account very seriously since this may have important impact within the stomach and in other organs (Fourmy *et al*., 2011). Commonly, physiological stress is quantified through the measurement of serum or salivary cortisol – an approach that may be too simplistic to provide a clear explanation or mechanistic basis (Davis *et al*., 2008) [2] Exercise-induced increase in endogenous cortisol may contribute to development of gastritis and gastric ulceration in sled dogs (Fergestad *et al*., 2016) [5]. Thorough knowledge of pathophysiology of gastritis in canines is required for greater understanding and development of new high throughput diagnostic and therapeutic approaches in canine gastric pathology. We have borrowed most of our guidelines from experiences in human medicine, but there is no certainity that the diseases we see in dogs are similar enough to justify this approach. It is important to evaluate the current therapeutic alternatives in the veterinary medicine.

Materials and Methods
The present study was conducted on six clinically healthy dogs and twenty dogs showing symptoms of gastritis irrespective of age and sex which were divided into two groups.
Group 1: Dogs (n=6) were having normal appetite, no history of vomiting, melena and abdominal pain. Blood sampling was done on the day of presentation.

Group 2: Dogs (n=20) were showing anorexia or inappetance, vomiting, melena, abdominal pain on the day of presentation. Blood sampling was done on the day of presentation.

Clinical observations: The important clinical parameters of all the dogs were recorded in the form of questionnaire i.e status of appetite (inappetance/anorexia), vomiting, haematemesis, melena and abdominal pain.
For haematological parameters, 3ml blood was collected aseptically from saphenous/ cephalic vein of each dog in EDTA vials. Samples were taken on the day of presentation (day 0). Haematological estimation was conducted immediately after the blood collection with haematology cell counter. Samples for serum separation were kept for one hour and then centrifuged at 3000 rpm for 10 minutes to separate plasma and serum.

The separated samples were stored at -20 °C until the estimation. Various biochemical parameters were estimated using semi-automatic clinical chemistry analyzer with ready to use kits from Coral, Tulip Diagnostic Limited. Gastrin and Cortisol levels were estimated by ELISA method using Canine specific ELISA Kit from Genxbio Health Sciences Pvt. Ltd.

The following parameters were estimated: haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC), total leukocyte count (TLC), differential leukocyte count (DLC), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, total plasma proteins, Cortisol, Gastrin, Pepsinogen A, Pepsinogen C. The statistical analysis of the data was done using software package for social sciences (SPSS) version 20 one way analysis of variance (ANOVA) and RM analysis at $P<0.01$ level of significance.

Results and Discussion

Based on clinical observation and history, all six healthy control dogs were having normal appetitie, no history of vomiting, melena and abdominal pain while all the twenty diseased dogs were showing anorexia or inappetance, vomiting (with blood in gastric contents (n=3), gastric contents with bile (n=4) and only gastric contents (n=13), melena (n=7), abdominal pain (n=11) on day of presentation.

Table 1: Clinical observation of healthy control and diseased dogs

Groups	Clinical signs and symptoms					
	Anorexia	Vomiting			Melena	Abdominal pain
		Gastric contents with blood	Gastric contents with bile	Gastric contents		
Group I (n=6)	Absent	Absent	Absent	Absent	Absent	Absent
Group II (n=20)	20	03	04	13	05	11

Gastric hyperacidity has been implicated as one of the major contributors to vomiting and gastric ulceration in dogs. These clinical signs include inappetence, weight loss, vomiting, hematemesis, and less commonly, diarrhea (Peters *et al.*, 2005) [12].

Mean±SE values of various haematological parameters of healthy control and diseased dogs on day of presentation are shown in table 2. In healthy control dogs Hb level (Mean±SE) was 12.16±1.06 g/dl. The Mean±SE value of Hb in diseased dogs was 14.06±0.37 g/dl which was significantly ($P<0.01$) higher than the healthy control dogs. Similarly the Mean±SE value of PCV of diseased dogs 41.06±0.89% was significantly ($P<0.01$) higher than the healthy control dogs 34.27±2.93%. Similar picture was observed in Mean±SE TEC value which revealed that, there was significantly ($P<0.01$) higher TEC value $6.60\pm0.17\times10^6$/µl in diseased dogs as compared to the TEC value of healthy control dogs ($5.26\pm0.51\times10^6$/µl). Comparative analysis of study revealed that there were no significant differences in the TLC and DLC parameters between healthy control and diseased animals.

Haemoconcentration as a consequence of dehydration due to vomiting may occur in cases of gastritis (Webb and Twedt, 2003; Ettinger and Fieldman, 2010) [20, 4]. Hematocrit may decrease in association with severe gastric erosions and ulcer disease due to acute or chronic blood loss. Microcytic and hypochromic anaemia also reported in different studies (Harvey *et al.*, 2008).There was no statistical significant difference reported in TLC and DLC values in the present study. Stanton and Bright. (1989) [17] also reported the 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) [6].

Table 2: Mean±SE values of Haematological parameters of Healthy control (Group I) and Diseased dogs (Group II)

Haematological parameters	Group I (n=6)	Group II (n=20)
Haemoglobin (g/dl)	12.16±1.06	14.06±0.37**
TEC (10^6/µl)	5.26±0.51	6.60±0.17**
PCV (%)	34.27±2.93	41.06±0.89**
TLC (10^3/µl)	7.98±0.47	9.18±1.26
DLC		
Neutrophils (%)	71.41±2.48	73.88±1.74
Lymphocyte (%)	23.33±2.86	22.32±2.09
Eosinophils (%)	2.45±0.56	2.19±0.99
Basophils (%)	0	0
Monocyte (%)	2.86±0.36	2.46±0.69

Means with different superscripts vary significantly *(P<0.01)*

Mean±SE values of various biochemical parameters of healthy control and diseased dogs on day of presentation are shown in table 3. There were no significant differences in the values (Mean±SE) of ALT, Total Protein, Creatinine and LDH between healthy control and diseased dogs. However in contrast to the present study, hypoproteinemia was a common finding and reflect blood loss, liver disease, renal disease, malabsorption, or combination of these diseases (Stanton and Bright, 1989) [17]. Only the BUN value (Mean±SE) of diseased dogs was significantly ($P<0.01$) higher than the healthy control dogs.

The Serum Cortisol value (Mean±SE) of diseased dogs was 5.59±1.90 µg/dl which was significantly ($P<0.01$) higher than that of healthy control dogs (0.25±0.05µg/dl) which reflects the sustained strain that the dogs experience with gastritis. The effects of "stress" are often cited as the cause of gastric ulcers in a variety of animals and circumstances. Commonly, physiological stress is quantified through the measurement of serum or salivary cortisol – an approach that may be too

simplistic to provide a clear explanation or mechanistic basis (Davis *et al*., 2008) [2]. Fergestad *et al*. (2016) [5] has proposed that exercise-induced increase in endogenous cortisol may contribute to development of gastritis and gastric ulceration in sled dogs. Various studies regarding sled dogs competing in the Iditarod race showed that dogs with abnormal gastroscopic findings after racing also had a significantly higher serum cortisol level, compared to dogs with normal gastroscopic findings (Philipp *et al*., 1992; O'Connor *et al*.,1995; Royer *et al*., 2005) [13, 10, 15].

Table 3: Mean±SE values of Biochemical Parameters in Healthy Control (Group I) and Diseased Dogs (Group II)

Parameters	Group I (n=6)	Group II (n=20)
ALT(IU/L)	57.61±4.52	53.16±3.66
LDH (IU/L)	110.32±5.21	132.09±8.82
Total protein(g/dl)	5.69±0.38	6.12±0.27
BUN(mg/dl)	17.71±1.36	29.32±1.44**
Creatinine(mg/dl)	0.59±0.84	0.63±0.10
Cortisol(µg/dl)	0.25±0.05	5.59±1.90**
Gastrin(ng/l)	21.04±3.10	15.95±4.75**
Pepsinogen A (µg/l)	5.91±0.41	10.82±1.13
Pepsinogen C (µg/l)	3.72±0.18	4.56±0.38
Pepsinogen A:C	1.60±0.14	2.61±0.33

Means with different superscripts vary significantly *(P<0.01)*

The results of estimation of serum Gastrin levels of healthy control and diseased dogs revealed that the serum gastrin level (Mean±SE) of diseased dogs (15.95±4.75 ng/l) was significantly lower ($P<0.01$) than the serum gastrin level (Mean±SE) of the healthy control dogs (21.04±3.10 ng/l). Comparative analysis of study revealed that there were no significant differences in the PGA, PGC and PGA: PGC parameters of healthy control and diseased dogs.

Serum Gastrin-17 levels were significantly lower ($P<0.01$) in diseased dogs as compared to the healthy control dogs which may be due to the negative feedback of increased acidity in gastric environment. It is the acidic gastric environment that normally would inhibit excessive gastrin secretion (Pounder and Smith, 1990; Bersenas *et al*., 2005; Parante *et al*., 2014) [14, 1, 11]. However some other researchers also reported that the mean level of gastrin 17 was the same in those with normal mucosa and antral gastritis, but increased with the extension of gastritis to the corpus and had its maximum level in those with corpus-predominant gastritis (Hay-sheykhoieslami *et al*., 2008) [8]. Gastrin hormone, whose major physiological effect is the stimulation of gastric acid secretion, seems to play an important role in all gastric inflammatory processes. In contrast to the present study, dogs with severe gastric lesions had significantly increased serum gastrin values compared with those without gastric lesions, presumably because the higher the number lesions in the stomach, the greater the stimulation of G cells (Garcia-Sancho *et al*., 2005). Serum gastrin concentrations were significantly increased in dogs with chronic lymphocytic-plasmacytic enteritis compared with those in dogs without gastrointestinal disease. Also, there was a positive correlation between the severity of the gastric lesion and the serum gastrin concentration (Garcia-Sanhco *et al*., 2005).Therefore, serum gastrin has become an important biomarker for gastric inflammation.

Comparative analysis of the present study revealed that there were no significant differences in the PGA, PGC and PGA:PGC parameters of healthy control and diseased dogs. These 2 enzymes, PGI and PGII, are measured as markers of advanced gastritis and PGI is the marker of gastric acid capacity. The mean concentration of PG A and PG C increases by the presence of any type of gastritis compared with those subjects with normal gastric mucosa (Samloff *et al*., 1975) [16]. It is believed that PG A is the predominant type of PG in dogs. An immunoassay for measurement of PGA concentrations may be a clinically useful, minimally invasive diagnostic tool for use in classifying gastric disorders in dogs (Suchodolski *et al*., 2002). Low serum PGA and a low PGA/PGC ratio have been recognized as useful diagnosis biomarkers for the corpus atrophic gastritis (AG) and for patients screening at high risk of gastric cancer. Serum indicators reflecting gastric function may correlate not only with primary diseases, but also with other extragastric diseases. Elevated serum PG concentrations should consider not only the gastric dysfunction but also abnormal renal function. Serum PG levels seems to be related to the morphologic and functional changes in the stomach, and their uses as "Serological biopsy" has been reported for over 20 years in medical sciences (Taggart and Samloff, 1987) [19]. Therefore, serum Gastrin-17 and Cortisol levels can be used as a sensitive biomarker in diagnosis of canine gastritis.

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