ejpmr, 2018,5(2), 32-38

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ENDOSCOPY DIAGNOSIS AND FOLLOW UP OF TREATMENT OF EXPERIMENTAL GASTRIC ULCER IN DOGS

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Article Received on 20/11/2017 **Article Revised on 11/12/2017** **Article Accepted on 02/01/2018**

1. ABSTRACT

Diagnosis and treatment of dog's gastrointestinal tract disorders have long been complicated. Endoscopy was used to examine the different grades of gastric ulcer in dogs experimentally and follow up response to acid suppressant drugs. Nine dogs were injected daily NSAIDs (diclofenac sodium and meloxicam) for 15 days for ulcer induction. Clinical, hematological, biochemical and histopathological examinations were carried out every 5 days parallel with endoscopic examination. Also, 3 dogs were undergoing treatment by acid suppressant drugs (ranitidine and omeprazole) for 14 days and follow up the response of treatment using endoscopy. The study revealed that the endoscope is the gold standard tool, more accurate and more sensitive than other methods for examination and follow up treatment of gastric ulcer in dogs.

KEYWORDS: Endoscope, Stomach, Ulcer, Induction, Treatment, Dogs.

2. INTRODUCTION

Diagnosis and treatment of dog's gastrointestinal tract disorders have long been complicated by the absence of clinical, histopathological, and therapeutic standards. In the last decades, medical endoscopy has emerged as a key technology for minimally-invasive examinations in numerous body regions and for minimally-invasive surgery in the abdomen, joints and further body regions.[1]

Gastric ulcers are one of the most frequently recognized disorders affecting the anterior segment of the gastrointestinal tract in dogs. The defect in mucosa that penetrates the muscularis mucosa is one of its affection. Gastric ulcer may be caused by various factors especially inflammatory conditions of non-steroidal and steroidal (glucocorticoid) inflammatory drugs for treatment of various diseases.[2]

A flexible endoscope is a valuable tool for the diagnosis of many small animal digestive tract diseases. This study provides a basic introduction to small animal gastrointestinal endoscopy including its diagnostic advantages for gastric ulcer as well as a prognostic value when follow up response to treatment. Occult disease as gastric ulcer is diagnosed by using endoscopic techniques. Other diagnostic tests such as blood chemistry; (Contrast) radiography may not be sensitive or specific enough to clearly identify the disorder.[3]

Diagnosis of gastric ulcer was done by several methods in the past years; traditional methods was made by evaluation of clinical manifestation, blood and histopathological examination[4,5] while recent diagnosis was done through endoscopic diagnosis and sometimes by X-ray and ultrasound examination.[6 7]

Gastric ulcer treatment has some sophisticated mechanism but the most reliable method for treatment is the inhibition of secretion of acid from the stomach through acid suppressant drugs such as proton pump inhibitor (omeprazole) and histamine-2 blocker (ranitidine).[8,9]

So, the aims of this study are to induction a model of gastric ulcer in dogs diagnosed by endoscope and confirm the result of endoscope through clinical, hematological, biochemical and microscopical evaluation. Also, treat the ulcer with acid suppressant drugs and follow up the response to treatment by endoscope.

3. MATERIAL AND METHODS

3.1 First Stage (Adaptation Period): Thirteen apparently healthy mongrel dogs (1-1.5 years old and 13.5-21 kg body weight) were selected and kept under observation for consecutive 15 days. Later on, these dogs were anesthetized by intravenous injection of atropine sulphate (0.01 mg/Kg) and xylazine HCL (2.332 mg/kg) as a pre-anaesthetic medication then ketamine HCL (20 mg/kg)[10] and subjected to endoscopic examination to

ensure normal gastric mucosa in the end of adaptation period.

3.2 Second Stage (Experimental induction and treatment of gastric ulcer): Five dogs was taken as a control group and ulcer was inducted to the remaining eight dogs by daily intramuscular injection two NSAIDs; meloxicam (MELOXICAM) ® 0.2 mg/kg and Diclofenac sodium (DICLO-5) ® 75 mg /dog/ for consecutive 15 days (Fig. 1).[11]

3.2.1 Clinical examination: Degree of body temperature, pulse and respiratory rates were recorded in addition to examination of mucous membranes and lymph nodes all over the experiment.[6]

3.2.2 Blood sampling: The whole blood (for haematological analysis) and serum samples (for gastrin using radioimmunoassay analysis**[14]** were taken before (control group), after induction of ulcer (5, 10 and 15 days) and after treatment. These samples were collected prior to anesthesia, at the same days of endoscopic examination.

3.2.3 Endoscopic procedures: Endoscopic examination was done 5, 10 and 15 days after ulcer induction to follow the changes in the gastric mucosa.

Endoscopic examination was done by video endoscope (ortascope) after deprivation of food for 6 to 8 hrs and water for 4 hrs, general anaesthesia was done to the dogs and placed in left lateral recumbency so that, the pylorus is up and the stomach can easily be examined.[3]

3.2.4 Treatment of gastric ulcer: Three dogs with ulcer (at day 10 after ulcer induction) were received two acid suppressant drugs; ranitidine **(Ranitidine)**® - histamine blocker (H2-RAs), 2 mg/kg, I/M daily and omeprazole **(Pepzole)**®- proton pump inhibitor (PPIs), 1 mg/kg, orally, each 12 hours for consecutive 14 days.**[12]** The endoscopic follow up was done at 3, 10 and 14 days of treatment.[13]

3.2.5 Histopathological samples: Gastric specimens were collected from dogs before (control), after ulcer induction and after treatment, at the days of endoscopic examination. One dog was euthanized at each period (control, 5, 10, 15 days after ulcer induction and after treatment) by injection of overdose of thiopental drug intravenously.[15] The specimen were rapidly fixed in 10% buffered formalin and processed in paraffin before staining by Hematoxyline and Eosin (H&E) and examined under microscope.[16]

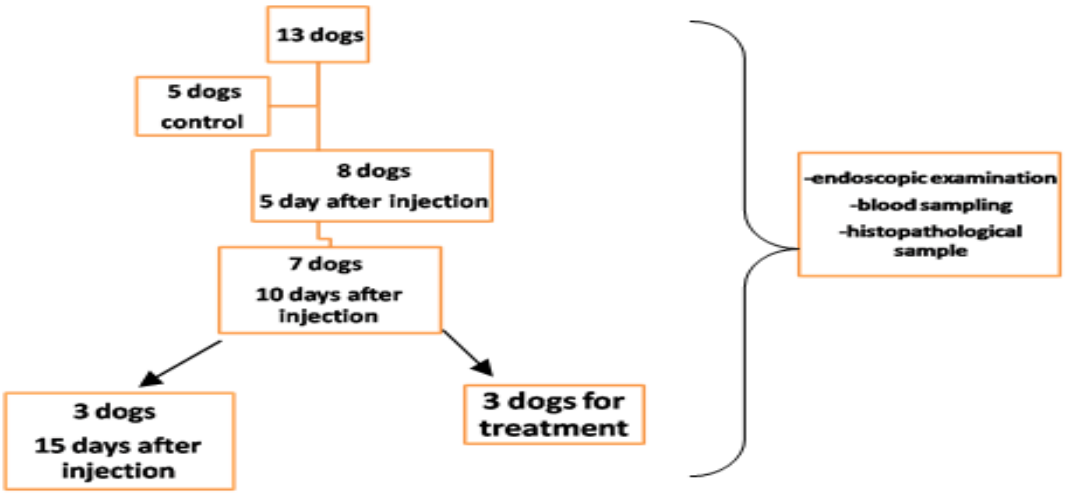

Fig. 1: Flow chart of experiment.

3.3 Statistical Analysis: Data were analyzed by ***SPSS (2001)*** software package, version 13 using one-way analysis of variance (ANOVA).

3.4 Ethical Considerations

All procedures of this study were carried out in accordance with the recommendations of the local ethics commission of the university. At the end of the experiment, dogs were euthanized by injection of an overdose of thiopental drug intravenously.[15]

4. RESULTS

4.1 Clinical examination: Clinical examination was recorded during the experiment; and revealed decrease in appetite, loss of body weight, melena, vomiting and some abdominal pain represented in the form of colic. Temperature, pulse and respiratory rate not significantly changed.

4.2 Endoscopic diagnosis

4.2.1 Zero degree of ulcer (normal mucosa)

The normal cardiac mucosa of the stomach appeared shiny, glistening and pale pink in color in some dogs and reddish pink in others while the body and pyloric part appeared darker than the cardia. Also, the rugea of the stomach was identified (Fig. 2).

Fig. 2: The normal mucosa of the stomach. The cardiac rugea before (a) inflating of air and after (b) inflating of air inside the stomach. The normal mucosa of the body and the pyloric part of the stomach before (c) air inflation and after (d) air inflation.

4.2.2 First degree of ulcer (pin point ulcer): after 5 days of injection of NSAIDs: Gastroendoscopy of dogs 5 days after injection of NSAIDs revealed mild lesion in the mucosa of the stomach represented in different form such as point ulcer, hyperemia located mainly in the cardiac orifice and the body of the stomach (Fig. 3).

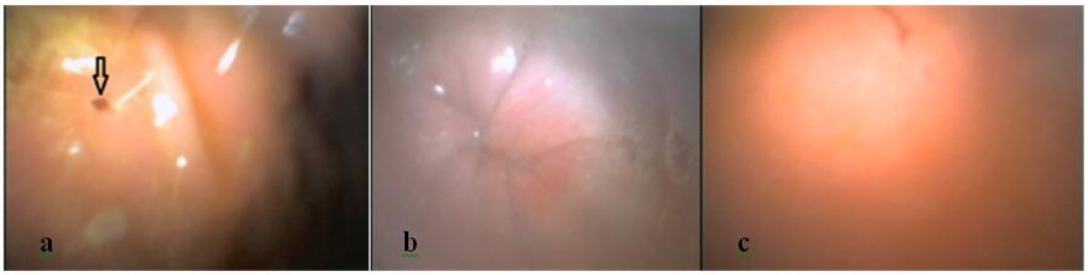

Fig. 3: The First degree of ulcer is represented in different forms. (a) Pinpoint ulcer (arrow) (b) Hyperemia in the cardiac opening. (c) linear small ulcer in the pyloric part.

4.2.3 Second degree of ulcer (Erosive gastritis): after 10 days of injection of NSAIDs: As the injection of NSAIDs was continued the lesions in the stomach were enlarged and become severe. The second degree of ulcer was identified in few and large lesions or multiple and small lesion distributed on the floor of the stomach (Fig. 4).

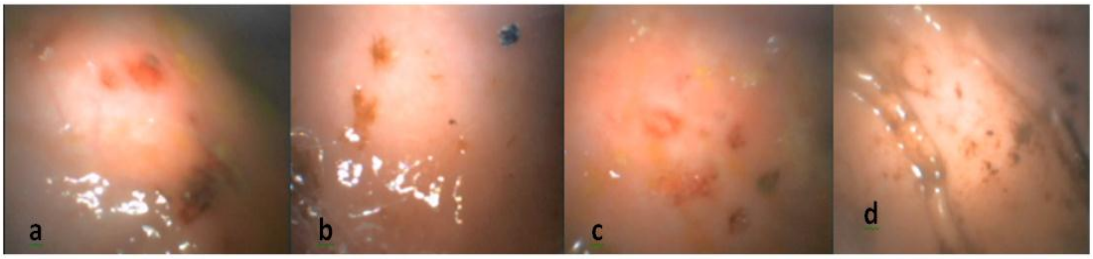

Fig. 4: The second degree of ulcer represented in the form of few large ulcers (a), (b) and (c) or showed as several points of hemorrhage (multiple small ulcer) (d).

4.2.4 Third degree of ulcer (ulcerative gastritis): after 15 days of injection of NSAIDs: Fifteen days after injection, more worse and obvious effect on the gastric mucosa appeared in the form of a huge ulcer in the body and pyloric part of the stomach or several hemorrhagic points on the surface and the floor of the stomach (Fig. 5).

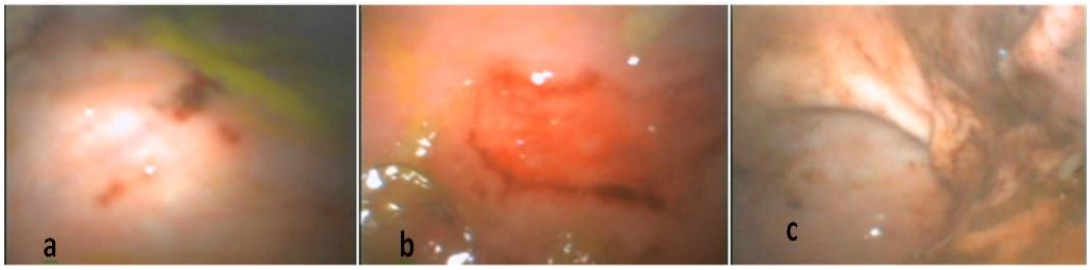

Fig. 5: The third degree of ulcer represented in form of very large single ulcer (a) and (b) or several hemorrhagic points of ulcer were distributed in the gastric wall (c).

4.3 Blood analysis: Hb level, RBCs count, PCV % and total number of platelets were significantly decreased (P≤ 0.05) 10 and 15 days after NSAIDs injection in comparison to values of control groups while the total number of WBCs was significantly increased (P≤ 0.05) 10 and 15 days after NSAIDs injection in comparison to values of control groups (Table 1). The mean value of serum gastrin was significantly increased (P≤ 0.05) 5, 10 and 15 days after ulcer induction in comparison to value of control group (Table 1).

Table. 1: Blood parameters of control group and ulcer groups.

Parameter	Control group	5 day after ulcer induction	10 day after ulcer induction	15 day after ulcer induction
Hb gm/dl	13.6±0.5[a]	13.0±0.5[a]	9.5±0.6[b]	7.7±0.7[c]
RBc *10[6]	4.7±0.4[a]	4.4±0.2[a]	3.3±0.2[b]	3.2±0.1[b]
PCV %	51.8±4.3[a]	47.8±3.7[a]	33.4±3.8[b]	25.3±1[c]
WBCs *1000	14 ±1041.5[a]	17±1507[a]	27±4803.6[b]	44±2089.5[c]
PLT*1000	323.2±23.7[a]	308.9±14.5[a]	262.6±22.8[b]	235.0±18[c]
Serum gastrin ng/l	38.7±1.3[a]	56.7±4.1[b]	227.1±9.9[c]	319.7±5.5[d]

Means within the same row carry different superscripts are significantly different (P≤ 0.05).

4.4 Histopathological changes

The severity of gastric inflammation usually has been graded by a simple 4-point scale (normal, mild, moderate, marked or severe) (Fig. 6).

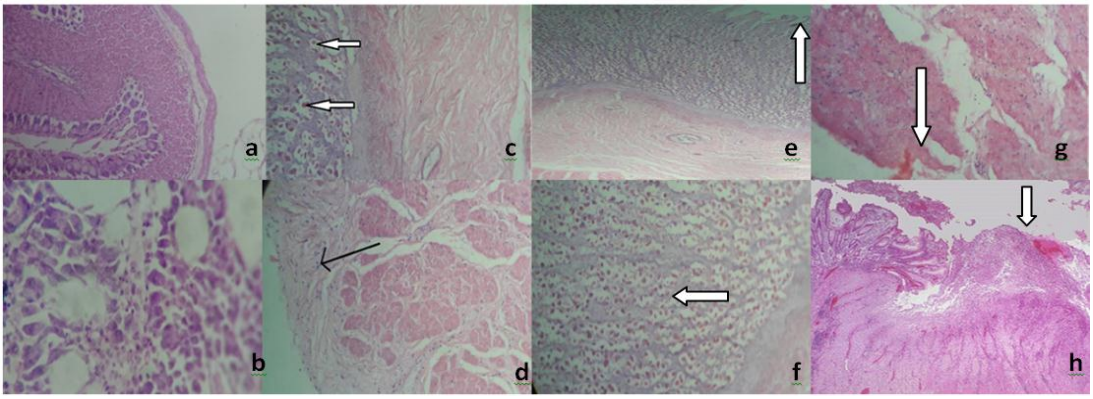

Fig. 6: Grade 1: (a) and (b) Normal gastric mucosa, intact cell membrane and regular arrange of epithelial cell and no cellular activity. Grade 2: (c) Mild gastritis, marked regional activity, (d) mild focal lymphocytic infiltration. Grade 3: (e) Moderate gastritis, with moderate regional activity and small erosion in the epithelium of gastric mucosa. (f) Fibroepithelial polyp.The stromal cells mildly enlarged and atypical. Grade 4: (g) and (h) Sever gastritis, with hyper-regional activity, ulcer granulation, inflammatory squamosal layer, marked cellular infiltration, and demarcated ulcer margin.

RESULTS OF TREATED GROUP

After treatment healing stages of gastric ulcer followed by endoscope were identified (Fig. 7). Healthy conditions of treated dogs were improved. All blood parameters and serum gastrin were significantly improved after treatment (Table 2).

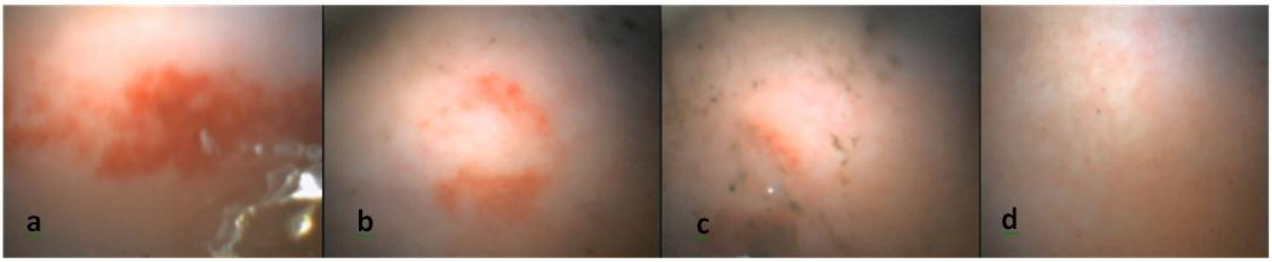

Fig. 7: Healing stages of gastric ulcer: (a) The gastric ulcer after 10 days of NSAIDs injection (second degree) shows massive erosion in the stomach wall. (b) At 3 days of treatment the center of the ulcer was disappeared, the ulcer margin begins to become less obvious and the erosive area was decreased. (c) At 10 days of treatment, the center of ulcer completely disappeared, but there was a small remnant of the margin. (d) At 14 days of treatment. The ulcer was completely disappeared and the gastric mucosa returns to normal.

Table. 2: Blood parameters of treated group compared to that before treatment.

Parameter	Before treatment (10 day after ulcer induction)	After the end of treatment
Hb gm/dl	9.5±0.6[a]	13.9±0.7[b]
RBc *10[6]	3.3±0.2[a]	4.8±0.2[b]
PCV %	33.4±3.8[a]	48.7±0.2[b]
WBCs *1000	27±4803.6[a]	1703±367[b]
PLT*1000	262.6±22.8[a]	304.7±9.5[b]
Serum gastrin ng/l	227.1±9.9[a]	41.8±3.2[b]

Means within the same row carry different superscripts are significantly different ($P \leq 0.05$)

Regeneration of the epithelial cells of the stomach wall and normal infiltration on mononuclear cells were reveled under the microscope (Fig. 8).

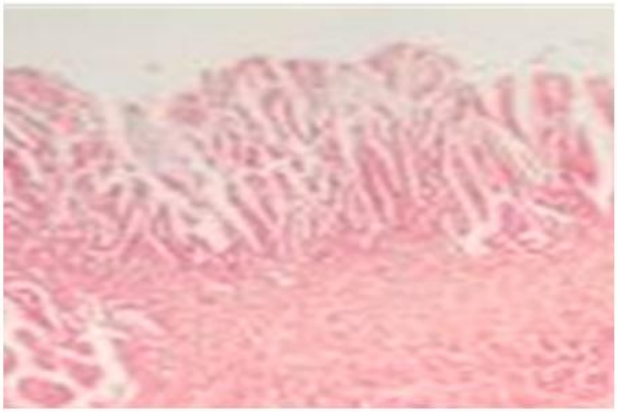

Fig. 8: Microscopical examination of the stomach specimen after treatment stained with H&E.

5. DISCUSSION

Examination of the gastric mucosa of dogs by an endoscope is valuable as it determines the different lesions in the stomach and classifies that according to its severity to four grades. An ulcer means 'epithelial loss' and depending on the depth, it can be superficial (erosion) or deep.[17]

This scoring system of gastric ulcer is the first grading in pet animals (according to our literature collected) and is similar to that scoring system of the equine gastric ulcer.[18] The current study identified characters for each grade of gastric ulcer similar to that recorded by Steffen and Cynthia.[3]

Normal mucosa (Zero degree): The gastric mucosa is smooth and reddish pink without any lesions. Overall, it is redder than the esophageal mucosa.

Pin point ulcer (First degree): small lesion may be in the form of mucosal hyperemia, usually localized in specific parts of the stomach and is probably the least reliable clue to gastric disease because color changes often represent vascular changes, but not mucosal disease in the stomach of dogs. They are more common for any reasons like hard food, small foreign body, NSAIDs injection as meloxicam or diclofenac.

Erosive gastritis (Second degree): Erosive gastritis is characterized by a thickening of the gastric mucosa with large rugal folds. Usually present in the form of multiple small erosions or it may be localized in the form of huge and severe erosion. Focal lesions often occur at the pyloric antrum and they may cause delayed gastric emptying.

Ulcerative gastritis (Third degree): Characterized by either a single large, deep ulcers surrounded by a firm raised wall and sometimes containing a fibrin plug or multiple, small, more superficial ulcers. Sever hemorrhage usually appear in this form due to injury of the blood vessels in the submucosa of the stomach.

Ulcers that occur as a consequence of administration of NSAIDs are shown by endoscope mainly in the antropyloric area. The same result was reported by Stanton and Bright.[2] And they are often with a punched out appearance and the walls were raised from the surrounding mucosa as detected by Sullivan and Yool.[19]

Not only endoscope helps in scoring lesion in the stomach, but also, makes early detection of the lesions. In our study, endoscope detected pin point ulcer only after 5 days of injection of NSAIDs where no one of the other methods of diagnosis detected it.

Clinical abnormalities recorded in this experiment were decreased appetite, abdominal pain, black tarry feces (melena), vomiting in some cases and loss of body weight considered general signs not specific for gastric ulcer.[2]

Hematemesis or melena, which is considered specific indicators of upper gastrointestinal bleeding not observed in the early stage of the ulcer, only appear when the gastric mucosa become severely hemorrhagic.[5]

The inflammatory process occurs in the gastric mucosa enhanced through leukocytic infiltration, especially neutrophils. So that there was marked leukocytosis with neutrophilia and thrombocytopenia in case of gastric ulceration.[20]

The PCV was monitored to assess whether any group of dogs had substantial dehydration due to severe blood loss and severe anorexia. It significantly decreased after 10 days after NSAIDs injection and this shown that PCV is

an unreliable monitoring tool for early, mild and acute gastrointestinal blood loss.[11]

Hematological findings usually are rarely specific for gastric ulcers as this may contribute to another disease.[17]

Serum gastrin was elevated 5 days after ulcer induction and become marked after 10 and 15 days of ulcer induction. So, serum gastrin used as an indicator for early detection of gastric lesion. But we cannot depend only on the serum gastrin level in the blood to detect gastric ulcer as it may be elevated in dogs with gastrinoma or decreased renal or hepatic clearance of gastrin hormone and this was reported previously by Jones et al.[21]

Canine histology of gastric lesions often shows strong similarities to their human counterparts. However, such conditions in the canine stomach are poorly studied and their cellular and molecular features are largely unknown. The current study reported different forms of histopathological classification of gastric inflammatory lesions in the canine and provide an update within the field of canine gastric pathology.

Histopathological examination was the bonier tool after an endoscope in the examination of gastric ulcer as they discuss fully the lesions observed in the stomach. Not only, describe the lesions, but also grade them in a systemic manner begin from the normal grade of the epithelial cell, passed with the mild, moderate and ended by the marked or severe lesion of the mucosa depending on area damaged on the mucosa, the amount of cellular infiltration and necrotic tissue present in ulcer. The disadvantage of this section (histopathology) is the need to scarify the animal to obtain the specimen and identify lesions.[19, 22]

After treatment, all parameters such as clinical signs, blood index and serum gastrin were returned to normal level due to changes in the stomach mucosa and returning to normal condition, these were demonstrated in the absence of pain, vomiting, diarrhea, anorexia and body condition. The three dogs were undergoing treatment after 10 days of ulcer induction as the second degree is optimal for treatment, after that the gastric mucosa is severely affected and hemorrhagic (as seen in the other 3 dogs reach 15 days of ulcer) and the routine treatment of acid suppressant isn't effective. And it is advised that when third degree of ulcer is detected, it needs immediate electrocautrization by endoscope to ulcer to avoid further bleeding. Endoscopic clips or epinephrine injection at the site of bleeding are also effective as those reported by the American Society for Gastrointestinal Endoscopy.[23]

The ulcer was recovered gradually; after 3 days of treatment, the ulcer becomes to disappear from the center to the periphery, after 10 days the center and periphery disappeared except some remnant in the margin, which completely disappeared after 14 days after treatment. These observations were similar to that reported by Parrah et al.[17]

6. CONCLUSION

Endoscope is the gold standard for diagnosis of gastric ulcer in dogs as it more sensitive, accurate and makes early detection of gastric lesion especially gastric ulcer. Also, endoscope act as a prognostic tool for the gastric ulcer diseases through following up the healing process of ulcer and so It determines if we complete the treatment or not!, to decrease the cost of treatment and hospitalization, This safer for the patient (dogs), owner and veterinarian.

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