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Effect of Certain Drugs on Treatment of Canine Pyometra with Special Reference to Kidney and Heart Function

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ABSTRACT

Pyometra, literally meaning pus in the uterus, is a disease of the uterus in intact, sexually mature bitches. The present study focuses on evaluation of different therapeutic protocol for treatment of canine pyometra based on haemato-biochemical parameters with special emphasis on kidney and heart function. A total of 18 female dogs were clinically diagnosed for pyometra at the department of Veterinary Gynaecology and Obstetrics, DUVASU, Mathura (U.P). These animals were divided into three Groups (Group II, III and IV) having 6 female dogs in each group and 6 healthy females were kept in Group I as control. All pyometra animals were treated with amoxicillin-clavulanic acid @ 25 mg/kg b.wt./day via intravenous route and intrauterine route for 9 days along with fluid therapy. Before giving hormonal treatment, all pyometra animals were treated with atropine @ 0.025 mg/kg b.wt and ondansetron @ 0.5 mg/kg b.wt. via intramuscular route. Cloprostenol @ 5 µg/kg b.wt on day 1, 3, 5, 7, 9 (subcutaneous route in Group II & IV and intravaginal route in Group III), tab mifepristone @ 2.5 mg/kg b.wt on day 2, 4, 6, 8 orally and tab cabergoline @ 5µg/kg b.wt on day 1, 2, 3, 4, 5, 6, 7, 8 orally provided in all pyometra groups. Nephroprotective drug having Taurine and N-Acetyl cysteine was given in Group IV for 14 days. Mean values of haemato-biochemical parameters altered significantly in canine pyometra. The therapeutic protocol in Group II, III and IV showed success rate of 83.33 and 66.63, 100%, respectively.

Keywords: Canine pyometra, Cabergoline, Cloprostenol, Electrocardiography, Kidney function.

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INTRODUCTION

Pyometra is a disease of diestrous phase frequently effecting middle to old age bitches. Pus is accumulated inside the progesterone primed uterus causing many local and systemic symptoms like inappetence to anorexia, fever, vomiting, pus coming from vagina, dehydration, polyuria, polydipsia, diarrhea, gait abnormality and abdominal pain on palpation. Hormonal aberrations followed by bacterial infection plays an important role in the etio-pathogenesis of the disease. It is generally considered that bacteria ascending from the normal vaginal flora proliferate in a progesterone-primed uterus (diestrous phase) and establish the infection (Hagman, 2012). In canine pyometra most commonly isolated bacteria species is *Escherichia coli*. Endotoxins produced by bacteria when present in circulation, interact with inflammatory and endothelial cells causing wide range of biological effects including elevation of heart and respiratory rates (VanMiert and Frens, 1968). Myocardial depression occurs due to severe sepsis and decreased blood supply to heart. Sinus tachycardia is the most common ECG finding in bitches with closed cervix pyometra (Santilli *et al*., 2019). Kidney failure occur due to decreased renal perfusion, immune-mediated glomerulonephritis, low ability for urinary concentration, interstitial tubular disease and decreased GFR. Renal excretory function is usually assessed by measuring serum creatinine when it is >1.8g/dl, around 66-75% of the nephrons are damaged while SDMA (symmetric dimethyl arginine) assess kidney damage much earlier than creatinine (Hall *et al*., 2014). At 40% kidney damage SDMA value (>14µg/dl) starts to rise in serum. Drugs for medical treatment could be progesterone-receptor antagonists (mifepristone), prostaglandin$F_{2\alpha}$ (cloprostenol) and dopamine agonists (cabergoline), or different combinations of these drugs (Fieni *et al*., 2014) in combination with antimicrobials.

MATERIALS AND METHODS

Total 18 female dogs with pyometra were clinically examined and diagnosed based on haematology and ultrasonography at department of Veterinary Gynaecology and Obstetrics, College of Veterinary Science and A.H., U.P. Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalya Evam Go Anusandhan Sansthan, Mathura (U.P). These 18 female dogs were randomly divided into 3 groups viz. Group II, III and IV (each group having 6 animals) based on route of administration of prostaglandin and 6 healthy animals were included in Group I as a healthy control.

For haematological studies, whole blood was collected in EDTA vial. Complete blood count of all blood samples was carried out by using a Nihon Kohden Celltac Alpha automated haematology analyzer. For biochemical studies, serum sample was collected and used for biochemical assays. Plasma concentration of BUN & Creatinine was estimated by AutoChemTM ingenious analyzer by using Arkray kits and SDMA by ELISA kit. All parameters were measured on day 0 and day 10 i.e. before and after the end of treatment. ECG was performed in all pyometra animals before the start of treatment.

In all 3 pyometra groups treatment was given with cabergoline @ 5 µg/kg/day orally for 9 days and mifepristone @ 2.5 mg/kg orally on day 2, 4, 6, 8. $PGF_{2\alpha}$ was given @ 5 µg/kg for 5 alternate days via SC route in Group II, intravaginal route in Group III and SC route along with Taurine (500mg) and N-Acetyl cysteine (150mg) orally in Group IV. These groups were made on the basis of route of administration of $PGF_{2\alpha}$. Before the start of treatment fluid therapy and antibiotic amoxycillin-clavulanic acid @ 25 mg/kg iv and intrauterine route was given in all pyometra groups. Atropine @ 0.025 mg/kg im was given to reduce the side effects of $PGF_{2\alpha}$ prior to hormonal therapy.

All data were expressed as mean±S.E. Statistical analysis was conducted by using Statistical Package for Social Science (SPSS, Version 20) to determine the difference between the groups. The comparison between the groups was analyzed by the unpaired student's t-test while the pre (day 0) and post-therapy (day 10) data was statistically analyzed by paired student's t-test. P values less than 0.05 were considered significant.

RESULTS AND DISCUSSION

The uterus was examined to evaluate pus pockets, nature of the content, irregularity of endometrium (Fig. 1).

Alterations in haemato-biochemical parameters were recorded in pyometra cases and healthy female dogs (Table 1 & 2). The mean values of total leucocyte count (TLC) and neutrophil percent was significantly ($P<0.001$) higher, and lymphocyte percent was significant ($P<0.001$) lower in pyometra affected animals as compared to the healthy control group. This alteration might be due to the leucocytosis with relatively increased neutrophils and decreased lymphocytes as observed due to diffuse suppurative inflammation of the uterus to combat infection, bone marrow inflammatory response and endotoxemia induced impaired immune response that may lead to a suppressive effect on lymphocyte activity (Lakshmikanth *et al*., 2016; Samantha *et al*., 2018).The mean values of haemoglobin were significantly lower in pyometra groups as compared to healthy control group. This might be due to the fact that female dogs with pyometra have anaemia due to erythro-

cytes diapedesis into the uterine lumen, reduced life span of circulating erythrocytes and suppression of erythropoiesis in the bone marrow associated with toxaemia. Loss of blood through the vaginal discharge in the open cervix pyometra might induce normocytic normochromic anaemia (Yu, 2012). Furthermore, platelet count in the present study was significantly (P<0.05) lower in pyometra affected females as compared to healthy control group. Thrombocytopenia may be attributed to the adverse effect of endotoxins on the bone marrow interfering in the synthesis of platelets.

The various serum biochemical parameters are presented in Table 2. The significant alterations were recorded in kidney function test. The mean values of blood urea nitrogen (BUN), Creatinine and SDMA were significantly (P<0.001) higher in pyometra affected bitches. This might be due to bacterial invasion stimulated the immune system to form immune complex at the basement membrane of the glomeruli causing an immune complex associated glomerulonephritis along with tubulo-interstitial inflammation led to renal dysfunction in pyometra affected bitches (Shah *et al*., 2016 ; Samantha *et al*., 2018).

The mean values of different hematological parameters were recorded at day 0 and day 10 and depicted in Table 1. Total leucocyte count and % neutrophil were significantly (P<0.05) decrease from day 0 to day 10 in all the treatment groups. Percent lymphocyte was significantly (P<0.001) increase from day 0 to 10 in all the treatment groups. This could be due to the evacuation of pus from the uterus by the effect of prostaglandin and antibiosis. The

Fig. 1: USG image showing severe distension of uterus with hyperechoic content.

Table 1: Haematological parameters in different pyometra groups on day 0 (before the start of treatment) and day 10 (after the end of treatment)

Groups	Days	Leucocytes ($10^3/\mu L$)	Neutrophils (%)	Lymphocyte (%)	TEC ($10^6/\mu L$)	Hb (g/dL)	Platelet ($10^3/\mu L$)
Group I (n=6)	Day 0	12.91±2.46	72.48±1.65	15.15±0.47	6.43±0.45	14.38±0.79	340.66±38.53
Group II (n=6)	Day 0	45.81±4.57	81.30±0.67	8.66±0.51	4.60±0.34	9.95±0.73	212.50±21.68
	Day 10	12.36±3.30*	70.93±2.71*	19.56±0.60**	5.24±0.17*	11.45±0.47*	330.33±42.34*
Group III (n=6)	Day 0	37.24±5.05	83.16±0.89	8.51±0.65	4.92±0.17	11.08±0.64	259.66±11.26
	Day 10	17.34±0.49*	77.73±1.11*	13.96±0.48*	5.86±0.22*	13.25±0.29*	357.33±16.60*
Group IV (n=6)	Day 0	55.45±6.15	88.85±0.23	7.06±0.26	4.50±0.22	8.21±0.22	166.83±38.32
	Day 10	15.85±5.66*	80.10±1.14**	13.03±0.34**	5.46±0.12*	10.85±1.95	277.32±23.04*

Mean within a column differ significantly (p**<0.001, p*<0.05)

present finding was supported by Shah *et al*., (2016) and Vijay *et al*., (2021). Hemoglobin content, TEC and platelet count were significantly (P<0.05) increase from day 0 to 10 in all the treatment groups. This might be due to the fact that reduction in septicemia/toxemia leads to bring down suppressive effect on erythropoiesis in the bone marrow along with other factors which are involved in anemia. This observation was commensurate with the previous reports by Shah *et al.,* (2016) and Vijay *et al*., (2021). This may be due to the reversal of toxemia had reduced adverse effects on thrombocytes. This study was supported by Shah *et al.,* (2016) and Vijay *et al*., (2021).

The mean values of different biochemical parameters were recorded at day 0 and day 10 and depicted in Table 2. Blood Urea Nitrogen, Creatinine and SDMA values were significantly (P<0.001) decreased from day 0 to 10 in all the treatment groups. This finding was supported by Shah *et al*., (2016) and Vijay *et al.,* (2021).

The maximum improvement was observed in Group IV in terms of kidney parameters as Taurine and N-acetyl cysteine reduced creatinine production from skeletal muscle, along with enhanced availability of nitric oxide (a potent vasodilator) to the site which led to increased blood supply to kidney and reduced burden on the kidney. These finding were in accordance with Shah *et al*., (2016) and Vijay *et al*., (2021). Both Taurine and N-acetyl cysteine possess antioxidant property. By reducing oxidative stress and inflammation, these substances may contribute to the protection of renal function.

Group III showed least improvement as confirmed by hematology, vaginal discharge in artificial insemination sheath and ultrasonography. Further treatment was extended in this group for 12-14 days and the biochemical parameters were reached to almost normal physiological range. The success of treatment was evaluated with improved activity and appetite, a change in the nature of discharge from hemorrhagic pus like to serous along with ultrasonography.

ECG recording was done for different parameters related to abnormal heart functioning (Table 3). In the present study, sinus arrhythmia was observed 33.33%; this could be in accordance with the suggestion that there is an alteration of triggered activity related to release of pro-arrhythmic factor

Table 2: Serum biochemical parameters of kidney in different pyometra groups on day 0 (before the start of treatment) and day 10 (after the end of treatment)

Groups	Days	BUN (mg/dL)	Creatinine (mg/dL)	SDMA (µg/dL)
Group I (n=6)	Day 0	22.25±2.58	0.99±0.16	11.52±0.57
Group Il (n=6)	Day 0	60.17±0.90	1.45±0.07	33.01±2.32
	Day 10	23.96±0.75**	0.74±0.05**	12.84±0.75*
Group III (n=6)	Day 0	57.87±2.56	1.37±0.14	28.13±1.25
	Day 10	21.06±0.93**	0.79±0.05*	16.43±0.87**
Group IV (n=6)	Day 0	163.30±1.75	5.30±0.05	37.31±2.07
	Day 10	24.14±1.01**	2.49±0.37**	13.74±0.95**

Mean within a column differ significantly (p**<0.001, p*<0.05)

Table 3: Abnormalities of rhythm and cardiac conduction in bitches affected with pyometra.

Abnormalities	Recorded in no. of bitches affected with pyometra	Per cent (%)
Type of rhythm		
Normal sinus rhythm (sinus arrhythmia)	6	33.33
Sinus tachycardia	5	27.77
Atrial fibrillation	1	5.55
Ventricular premature complexes	2	11.11
Ventricular tachycardia	1	5.55
Conduction abnormalities		
Left bundle branch block	4	22.22
ST depression	2	11.11
First degree AV block	0	0
Second degree AV block	0	0
Electrical alternans	0	0

during the SIRS, including high catecholamine levels (Werdan *et al*., 2009). Sinus tachycardia was observed as 27.77% and this could be due to increased metabolic demand, severe anaemia, shock, and sepsis. Atrial fibrillation was found 5.55% and it is a rapid and uncoordinated atrial activation that paralyzes the atrium itself (Santilli *et al*., 2019).

In the present study, ventricular premature complex (VPCs) was observed 11.11%. In dogs, VPCs could be the combined result of multiple factors including myocyte oxygen deficiency, myocardial damage and endotoxemia that can occur in bitches with pyometra (Santilli *et al.,* 2019). Ventricular tachycardia and left bundle branch block were recorded as 5.55% and 22.22%, respectively. ST depression was recorded to be 11.11% and this may be due to several reasons such as lack of oxygen to the myocardium, pericarditis, myocarditis, hyperkalaemia, ischemia, intraventricular conduction delay, and hypertrophy of the left ventricle (Santilli *et al*., 2019). In the present study, low voltage QRS was found in 3 animals out of 18 and prolonged QRS duration was found in 8 animals out of 18. These findings could be due to the presence of excess of fluid in the uterus, damping the electrical signal as described in the pleural effusion, peripheral edema and ascites (Fries, 2003; Madias, 2008).

CONCLUSIONS

The different treatment protocols showed success rate of 83.33, 66.63 and 100% in Group II, III and IV respectively. In pyometra affected cases hematology revealed leukocytosis along with neutrophilia and lymphocytopenia. Anemia was evident by decreased TEC, hemoglobin concentration. Increased values of BUN, Creatinine and SDMA indicate the decreased efficiency of kidneys to remove nitrogenous wastes from circulation. Group IV having $PGF_{2\alpha}$ S/c route, prolactin inhibitor, anti-progesterone agents and nephroprotective agents showing maximum beneficial effect and recovery of pyometra as revealed by USG and hematology after the end of treatment. Group III having $PGF_{2\alpha}$ via intravaginal route showed minimal/no side effect but duration of treatment was prolonged.Cardiac arrhythmias and abnormalities on ECG recording were suggestive of myocardial injury.

CONFLICT OF INTEREST

None.

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