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Evaluation of different therapeutic protocols for treatment of pyometra in bitches

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Abstract
Pyometra is a potentially life threatening condition which requires an early diagnosis to conserve the life of the animal. The analysis of various parameters helps in the assessment of the clinical status of the bitches. This study was undertaken on canine pyometra and consisted of 12 bitches of different breeds with known breeding history and open type of pyometra. The haematological and biochemical parameters were evaluated before and at the end of treatment. The clinical cases were divided randomly into two different groups with each group consisting of six bitches. The bitches in the two groups were treated using synthetic PGF2α along with antibiotics and second group was treated with dopamine agonist prolactin inhibiting drug, *i.e.,* (Cabergoline) along with combination of a synthetic PGF2α (Cloprostenol).Treatment of canine pyometra by the use of different drugs was found to be successful. Treatment of canine pyometra using a combination of a dopamine agonist prolactin inhibiting drug (Cabergoline) and a lower dose of synthetic PGF2α (Cloprostenol) was found to be the most effective method among the two therapeutic protocols used in the present study.

Keywords: Pyometra, bitches, treatment, synthetic prostaglandin, cabergoline, side effects

Introduction
Pyometra is a common metoestrual disease of intact bitches with systemic illness (Borresen and Skrede, 1980; Sevelius *et al.*, 1990) [2, 9]. An exaggerated response of the uterine mucosa to chronic progestational stimulation during the luteal phase due to altered oestrogen-progesterone receptors leads to cystic endometrial hyperplasia with excess secretions in the uterine lumen and secondary bacterial infection particularly of *E. coli* from vagina that liberate endotoxin leading to organ damage (Gayakawad *et al.*, 1999; Hagman, 2004) [6, 7]. Progesterone inhibits uterine contractions, responsible for the cervical closure has negative effects on uterine immunity while protecting against infections and facilitating uterine secretion and cystic endometrial development. Therefore, during the treatment of pyometra the effects of progesterone should be inhibited either directly by luteolysis using prostaglandins or indirectly either by using a dopamine agonist which induces functional arrest and finally luteolysis of the corpus luteum (CL) through inhibition of prolactin or by using a progesterone receptor antagonist such as aglepristone which prevents progesterone binding to its receptors (Verstegen *et al.*, 2008) [11]. Therefore, present study was undertaken to investigate the alterations in clinical, haematological and blood biochemical profiles of bitches infected with open pyometra before and after treatment.

Materials and Methods
The study was carried out at the Department of Veterinary Gynaecology and Obstetrics, CVSc, Rajendranagar, Hyderabad. Twelve clinical cases of different breeds in the age group of two to twelve years that were brought during the period of January 2017 to November 2017 with breeding history or with clinical symptoms indicative of the open type pyometra were taken for the study. The pyometra was further confirmed using diagnostic methods like abdominal palpation, radiography and ultrasonography. Bitches were divided into two groups each consisting of six bitches and subjected to different treatment protocols. Group I bitches were treated with synthetic $PGF_2\alpha$ i.e. cloprostenol sodium** (Inj Vetmate™, 2 ml each ml contain 250 µg cloprostenol Vetcare® Divn. Thane, Maharashtra, India) @ 1 µg/kg Bwt SC every 48 hrs even 2-3 days after complete cessation of pus discharge from vagina along with a course of

antibiotic and supportive therapy. Group II bitches were treated with combination of synthetic $PGF_2\alpha$ i.e. cloprostenol sodium** (Inj Vetmate™, 2 ml each ml contain 250 µg cloprostenol Vetcare® Divn. Thane, Maharashtra, India) @ 1 µg/kg Bwt SC every 48 hrs for 2 administrations, later dopamine agonist which decreases hormone levels i.e. cabergoline*** (Tab Cabgolin® 0.25 mg contain cabergolin in each tablet, Sun Pharma, Sikkim, India) @ 5 µg/kg Bwt PO until complete cessation of pus discharge from vagina along with antibiotic supportive therapy depending upon the condition of the case was given. The physiological, haematological and biochemical parameters were studied before 0^{th} day and after end of treatment. Therapeutic efficacy was assessed in terms of the return of abnormal parameters to either normal or near to normal values as compared to both groups and intensity of side effects.

Results

All the animals affected with pyometra showed clinical signs consisting of lethargy, depression, inappetance, anorexia, polyuria, polydipsia, vomiting and abdominal distension along with muco purulent vaginal discharge. Before starting the treatment protocol, physiological parameters like rectal temperature and respiration rate were elevated in all the groups of bitches. These parameters were further elevated in the group I treated bitches whereas there was a significant decrease in the levels of these parameters in the group II treated bitches. Treatment response was found to be 100% in group II bitches treated with combination of cloprostenol and cabergoline as compared to the bitches treated with cloprostenol along with antibiotic. Therapeutic efficacy was evaluated based on several factors. Prior to treatment, levels of haematological parameters like Hb, PCV, TEC and lymphocyte count and biochemical parameters like mean alanine transaminase in serum were lower than the normal value in all the groups of bitches affected with pyometra. The levels of these parameters were increased significantly in the treatment groups. There was a significant increase in the levels of haemoglobin, PCV, TEC, lymphocytes and mean alanine transaminase in the serum of the group of bitches treated with combination of cloprostenol and cabergoline as compared to the bitches treated with cloprostenol along with antibiotic. Before treatment the levels of haematological parameters like neutrophils and monocytes and biochemical parameters like blood urea nitrogen, creatinine, aspartate transaminase, and alkaline phosphatase were higher than the normal value. The levels of these parameters were decreased significantly in the treatment groups. A significant decrease was observed in the group of bitches treated with combination of cloprostenol and cabergoline as compared to the bitches treated with cloprostenol along with antibiotic alone. All the values of the above parameters are presented in Table 1 and 2. The bitches treated with cloprostenol showed a severe degree of side effects whereas in other group, side effects were moderate. The side effects observed in each group are listed in Table 3.

Table 1: Physiological, Haematological and Biochemical parameters in different groups of bitches affected with pyometra before treatment.

Parameters		Group I Mean± SE	Group II Mean± SE
Physiological parameters	Rectal temperature (^{0}F)	103.05±0.14	103.45±0.27
	Heart rate (per minute)	111.66±1.42	114.83±1.77
	Respiration rate (per minute)	31.33±0.76	31.00±0.57
Haematological parameters	Haemoglobin (gram %)	8.66±1.15	11.45±1.37
	PCV (%)	32.16±2.56	31.08±2.55
	TEC (× 10^6/µl)	4.05±0.40	4.45±0.65
	MCV (fl)	65.40±3.81	67.51±1.97
	MCH (pg)	20.86±0.97	22.55±0.48
	MCHC (%)	29.88±1.47	32.18±0.60
	TLC (× 10^3/µl)	39.81±0.40	37.63±1.13
	Neutrophil (%)	79.65±0.38	77.68±0.90
	Lymphocyte (%)	10.56±0.26	10.65±0.34
	Monocyte (%)	9.91±0.45	8.95±0.24
	Eosinophil (%)	2.93±0.05	2.82±0.14
Biochemical parameters	BUN (mg/dl)	29.01±0.64	23.60±1.18
	Creatinine (mg/dl)	2.26±0.12	2.08±0.04
	AST (U/L)	48.91±0.76	49.24±0.55
	ALT (U/L)	26.81±0.76	29.09±0.72
	ALP (U/L)	157.26±1.27	156.55±0.80

Table 2: Physiological, Haematological and Biochemical parameters in different groups of bitches affected with pyometra after treatment.

Parameters		Group I Mean ±SE	Group II Mean ±SE
Physiological parameters	Rectal temperature (^{0}F)	102.73±0.11^a	102.85±0.20^b
	Heart rate (per minute)	109.50±1.60^a	111.16±2.10^a
	Respiration rate (per minute)	28.83±1.10^a	28.66±0.66^a
Haematological parameters	Haemoglobin (gram %)	16.95±0.33^a	17.36±0.21^b
	PCV (%)	42.36±0.51^a	41.80±0.72^a
	TEC (× 10^6/µl)	6.60±0.07^a	6.80±0.19^b
	MCV (fl)	75.03±1.39^a	71.30±1.68^a
	MCH (pg)	24.06±1.12^a	25.68±0.66^a
	MCHC (%)	32.88±0.92^a	34.35±0.70^a
	TLC (× 10^3/µl)	16.40±0.31^b	14.70±0.70^a
	Neutrophil (%)	68.53±0.44^b	65.76±1.26^a
	Lymphocyte (%)	29.03±0.19^b	27.81±0.42^a
	Monocyte (%)	8.45±0.48^a	7.00±0.62^a
	Eosinophil (%)	3.02±0.12^b	2.50±0.24^a
Biochemical parameters	BUN (mg/dl)	20.87±0.57^b	17.44±0.60^a
	Creatinine (mg/dl)	1.88±0.01^b	1.87±0.01^b
	AST (U/L)	44.14±0.51^b	38.78±0.41^a
	ALT (U/L)	34.30±1.07^a	37.02±0.70^b
	ALP (U/L)	137.63±1.28^b	122.65±0.85^a

Means bearing different superscripts of Anova test row wise differs significantly (P< 0.05) between the groups before and after treatment.

Table 3: Side effects observed after administration of $PGF_2\alpha$ either alone or in combination with cabergoline for treatment of pyometra in bitches.

Side effects	Group I		Group II	
	No. of animals	Percentage	No. of animals	Percentage
Salivation	2	33.33	Nil	Nil
Vomition	4	66.66	3	50.00
Panting	3	50.00	2	33.33
Restlessness	2	33.33	3	50.00
Hyperpnoea	3	50.00	2	33.33
Defaecation	4	66.66	3	50.00
Urination	Nil	Nil	Nil	Nil

Discussion

All the two groups of bitches were successfully treated using different treatment protocols resulting in 100% recovery rate in each group. Similar findings were reported by England *et al*., (2007) [4]; Verstegen *et al.,* (2008) [11]; Shukla (2012) [10]; Jena *et al*., (2013) [8] and Ahmed *et al.,* (2015) [1]. There was 100 per cent recovery rate observed in the bitches treated with combination of cloprostenol and cabergoline at the end of treatment. Corrada *et al.,* (2006) [3] and Jena *et al*., (2013) reported 83 per cent and 100 per cent recovery rate respectively by using combination of cloprostenol and cabergoline treatment for open pyometra. Corrada *et al.,* (2006) [3] and Verstegen *et al.,* (2008) [11] reported by clinical recovery after treatment of the bitches using combination of cloprostenol and cabergoline might be due to synergistic effect of dopamine agonistic act on the cabergoline reduced prolactin secretion which is luteotropic in bitches and combination of $PGF_2\alpha$ resulted in the rapid luteolysis. However, Ahmed *et al.,* (2015) [1] reported that the treatment of pyometra using lower dose of synthetic $PGF_2\alpha$ (cloprostenol) and cabergoline was found to be successful. $PGF_2\alpha$ treatment results in contraction of myometrium (immediate effect), luteolysis (delayed effect) and relaxation of cervix (least consistent effect) because of this type of action of cloprostenol it is not advised for treatment of closed pyometra bitches. (Shukla (2012) [10]

Fieni (2006) [5] who used repeated administration of low dose cloprostenol in treatment of open or closed pyometra and Jena *et al.,* (2013) [8] who successfully treated by using synthetic $PGF_2\alpha$ i.e. Cloprostenol sodium @ 1 µg/kg Bwt. All the above effects might be due to the fact that $PGF_2\alpha$ caused myometrial contraction causing expulsion of exudates from uterus and also inhibited synthesis of progesterone from corpus luteum by its luteolytic effect. Corrada *et al*., (2006) [3] and Verstegen *et al.,* (2008) [11] reported that cloprostenol had longer half-life of 48 hrs and less dose i.e. 1 µg/kg Bwt, so large dose of $PGF_2\alpha$ is not significant to cause luteolysis on single administration due to less $PGF_2\alpha$ on CL, so that it has to be given in small quantity in multiple doses to regress the corpus luteum and evacuation of pus in pyometra cases of bitches unlike in other farm animal.

Side effects have been shown to be dose dependent and to diminish with repetition of treatment (Verstegen *et al.,* (2008) [11]. This might be due to low dose of synthetic $PGF_2\alpha$ analogue used for treatment. These findings were in agreement with the findings of Fieni (2006) [5] and Jena *et al*., (2013) [8]. Side effects observed might be due to poor general condition of the bitches as reported by Fieni (2006) [5] or might due to parasympathetic action of prostaglandin resulting in contraction of smooth muscle of gastrointestinal tract, increased respiration and salivary secretion. However, no side effects were observed after administration of cabergoline alone indicating that whatever side effects observed might be due to the effect of low dose cloprostenol as reported by England *et al*., (2007) [4]; Shukla (2012) [10] and Jena *et al*., (2013) [8]. These findings were in accordance with the reports of Corrada *et al*., (2006) [3] who reported that mild digestive side effects (Diarrhoea and vomiting not requiring treatment) after administration of cloprostenol probably due to the relatively low dose used for the $PGF_2\alpha$. Treatment of canine pyometra using a combination of a dopamine agonist prolactin inhibiting drug (Cabergoline) and a lower dose of synthetic PGF2α (Cloprostenol) was found to be the most effective method among the two therapeutic protocols used in the present study.

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