Comparative efficacy of various therapeutic protocols in the treatment of pyometra in bitches

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ABSTRACT: This study was undertaken on canine pyometra and consisted of 28 bitches of different breeds with known breeding history and open type of pyometra. The diagnosis of pyometra was made by correlating the history and clinical signs with the findings of abdominal palpation, radiography and ultrasonography. The physiological, haematological and biochemical parameters were evaluated before and at the end of therapy. The clinical cases were divided randomly into four different groups with each group consisting of seven bitches. One untreated control group in which bitches were given only supportive therapies was included. The bitches in the other three groups were treated using natural $PGF_2\alpha$ or synthetic $PGF_2\alpha$ or a combination of a dopamine agonist prolactin-inhibiting drug, i.e., cabergoline and lower dose of synthetic $PGF_2\alpha$ (Cloprostenol) along with supportive therapies. Treatment of canine pyometra by the use of different drugs was found to be successful. Though a lower dose of cloprostenol was effective in treating pyometra, it is not recommended due to high rates of recurrence and lower conception rates. Treatment of canine pyometra using a combination of a dopamine agonist prolactin-inhibiting drug (Cabergoline) and a lower dose of synthetic $PGF_2\alpha$ (Cloprostenol) was found to be the most effective method among the three therapeutic protocols used in the present study.

Keywords: pyometra; treatment; natural prostaglandin; synthetic prostaglandin; cabergoline; side effects; recurrence rate; conception rate

List of abbreviations

PCV = packed cell volume, **TEC** = total erythrocyte count, **BUN** = blood urea nitrogen

Pyometra, a hormonally mediated acute or chronic polysystemic diestrual disorder, is the most common genital disease in bitches and results in high mortality if not treated (Singh et al. 2010). It is recognised as one of the main causes of disease and death in the bitch (Coggan et al. 2008) and is a common disease in countries where the routine spaying of young dogs is not common practice (Pelander et al. 2008). 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). The most important hormone regulating the corpora lutea of bitches is prolactin, which is luteotrophic in nature. Repeated administration of prolactin inhibitors more than 25 days after ovulation can result in a rapid and permanent reduction in plasma progesterone concentrations (Onclin et al. 1993), an effect that has been used to terminate pregnancy.

MATERIAL AND METHODS

The present work was carried out at the Department of Animal Reproduction, Gynaecology and Obstetrics, College of Veterinary Science, Rajendra-

nagar, Hyderabad. Twenty eight clinical cases of different breeds in the age group of one to twelve years that were brought to the Animal Reproduction, Gynaecology and Obstetrics Unit, Teaching Veterinary Clinical Complex, Bhoiguda and Campus Hospital, College of Veterinary Science, Rajendranagar, Hyderabad with known breeding history or with clinical symptoms indicative of the open type of pyometra were taken for the study. The pyometra was further confirmed using diagnostic methods like abdominal palpation, radiography and ultrasound examination. Bitches were divided into four groups each consisting of seven bitches and subjected to different treatment protocols. Group I bitches were treated only with supportive therapies (control group). Bitches in Group II, were treated with natural $PGF_2\alpha$, i.e., dinoprost tromethamine (Lutalyse™, Pfizer Limited, Mumbai, India) at the dose rate of 100 µg/kg body weight subcutaneously once daily for seven days with supportive therapies. Bitches in Group III were treated with synthetic $PGF_2\alpha$, i.e., cloprostenol sodium (Vetmate™, Vetcare® Divn., Thane, Maharashtra, India) at the dose rate of 1 µg/kg body weight subcutaneously once daily for seven days with supportive therapies. Bitches in Group IV were treated with a combination of a dopamine agonist prolactin-inhibiting drug, i.e., cabergoline (Cabgolin® 0.25, Sun Pharma, Sikkim, India) at the dose rate of 5 µg/kg body weight once daily orally and synthetic $PGF_2\alpha$ i.e. cloprostenol sodium (Vetmate™, Vetcare® Divn., Thane, Maharashtra, India) at the dose rate of 1 µg/kg body weight subcutaneously once daily for seven days with supportive therapies. The physiological, haematological and biochemical parameters were studied before (0^{th} day) and

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

Parameters		Group I	Group II	Group III	Group IV
Physiological parameters	rectal temperature (°F)	102.83 ± 0.28	103.2 ± 0.28	103.5 ± 0.36	102.94 ± 0.35
	heart rate (per min)	112.00 ± 4.00	110.43 ± 4.07	107.28 ± 4.00	110.57 ± 3.22
	respiration rate (per min)	29.57 ± 1.15	30.71 ± 1.32	29.86 ± 1.75	30.28 ± 1.32
Haematological parameters	haemoglobin (gram%)	11.0 ± 0.32	11.08 ± 0.38	11.08 ± 0.42	11.10 ± 0.28
	PCV (%)	33.83 ± 0.92	34.07 ± 1.06	34.24 ± 1.18	34.03 ± 0.89
	TEC ($\times 10^6$/µl)	5.48 ± 0.17	5.54 ± 0.89	5.51 ± 0.21	5.51 ± 0.14
	MCV (fl)	66.88 ± 0.52	66.30 ± 0.63	66.44 ± 0.77	66.36 ± 0.54
	MCH (pg)	21.44 ± 0.32	21.91 ± 0.48	21.41 ± 0.28	21.13 ± 0.47
	MCHC (%)	31.48 ± 0.27	31.34 ± 0.40	31.30 ± 0.28	31.64 ± 0.41
	TLC ($\times 10^3$/µl)	33.27 ± 7.74	33.44 ± 6.89	36.63 ± 9.58	35.56 ± 8.36
	neutrophil (%)	76.86 ± 1.06	79.00 ± 0.62	79.57 ± 1.02	78.28 ± 2.37
	lymphocyte (%)	11.14 ± 0.94	9.71 ± 0.52	8.86 ± 0.74	11.00 ± 1.43
	monocyte (%)	9.86 ± 0.51	9.00 ± 0.49	9.00 ± 0.31	8.43 ± 0.84
	eosinophil (%)	2.14 ± 0.40	2.28 ± 0.18	2.57 ± 0.29	2.28 ± 0.28
Biochemical parameters	BUN (mg/dl)	26.28 ± 1.47	23.43 ± 1.17	24.28 ± 1.67	24.00 ± 0.97
	creatinine (mg/dl)	2.10 ± 0.08	2.14 ± 0.07	2.06 ± 0.09	2.20 ± 0.08
	AST (IU/l)	49.14 ± 1.24	49.00 ± 1.23	48.71 ± 1.34	50.28 ± 1.86
	ALT (IU/l)	28.28 ± 2.09	26.00 ± 2.72	25.00 ± 1.92	29.71 ± 1.71
	ALP (IU/l)	153.43 ± 5.83	156.57 ± 7.65	154.71 ± 5.77	155.43 ± 6.95
	TP (g/dl)	7.94 ± 0.27	8.01 ± 0.34	8.10 ± 0.39	8.06 ± 0.37
	albumin (g/dl)	2.91 ± 0.09	2.98 ± 0.26	2.93 ± 0.13	2.84 ± 0.22
	globulin (g/dl)	5.03 ± 0.27	5.03 ± 0.27	5.17 ± 0.29	5.21 ± 0.31
	total bilirubin (mg/dl)	0.46 ± 0.06	0.47 ± 0.08	0.43 ± 0.07	0.48 ± 0.07

Group I = control group

after treatment (8th day). Attempts were made to contact the owners of the bitches that recovered after various treatments to obtain follow up data. All the data pertaining to post-treatment return to oestrus, breeding, conception and recurrence were obtained. Therapeutic efficacy was assessed in terms of the return of abnormal parameters to either normal or near-normal values as compared to the untreated control group, intensity of side effects and post treatment reproductive status. All bitches in the control group and recurred bitches had undergone ovariohysterectomy.

RESULTS

Treatment response was found to be 100% in each group though different therapeutic protocols were used to treat the pyometra. Therapeutic efficacy was evaluated based on several factors. Prior to treatment, there was no significant difference between the four groups of bitches with respect to physiological, haematological and biochemical parameters. 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 untreated control group bitches whereas there was a significant decrease in the levels of these parameters in the treatment groups. A significant decrease was observed in bitches treated with the combination of cloprostenol and cabergoline as compared to the bitches treated with either dinoprost tromethamine or cloprostenol alone. Prior to treatment, levels of haematological parameters like haemoglobin, packed cell volume (PCV), total

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

Parameters		Group I	Group II	Group III	Group IV
Physiological parameters	rectal temperature (°F)	103.34 ± 0.18^a	102.41 ± 0.13^b	102.31 ± 0.27^b	101.67 ± 0.12^c
	heart rate (per min)	109.86 ± 2.23^a	110.00 ± 3.08^a	105.71 ± 2.34^a	106.28 ± 2.08^a
	respiration rate (per min)	32.00 ± 0.90^a	24.86 ± 0.88^b	24.57 ± 0.92^b	20.57 ± 0.29^c
Haematological parameters	haemoglobin (gram%)	10.70 ± 0.29^c	12.40 ± 0.25^b	12.37 ± 0.28^b	13.38 ± 0.33^a
	PCV (%)	33.30 ± 0.90^c	37.67 ± 0.89^b	37.98 ± 0.97^b	40.83 ± 1.09^a
	TEC (× 10^6/µl)	5.33 ± 0.14^c	6.17 ± 0.14^b	6.18 ± 0.14^b	6.68 ± 0.17^a
	MCV (fl)	66.77 ± 0.51^a	67.37 ± 0.42^a	67.96 ± 0.51^a	67.34 ± 0.43^a
	MCH (pg)	21.14 ± 0.31^a	22.16 ± 0.45^a	21.60 ± 0.28^a	21.30 ± 0.48^a
	MCHC (%)	31.28 ± 0.27^a	31.48 ± 0.40^a	31.46 ± 0.27^a	31.84 ± 0.39^a
	TLC (× 10^3/µl)	34.14 ± 7.76^a	14.16 ± 2.76^b	14.31 ± 2.16^b	11.46 ± 2.63^b
	neutrophil (%)	78.00 ± 0.97^a	69.43 ± 0.78^b	69.86 ± 0.63^b	65.71 ± 0.81^c
	lymphocyte (%)	10.00 ± 0.92^c	21.57 ± 0.78^b	20.28 ± 0.42^b	26.14 ± 0.86^a
	monocyte (%)	10.28 ± 0.52^a	7.14 ± 0.40^b	7.43 ± 0.20^b	5.71 ± 0.28^c
	eosinophil (%)	1.71 ± 0.28^a	1.86 ± 0.26^a	2.43 ± 0.20^a	2.43 ± 0.20^a
Biochemical parameters	BUN (mg/dl)	29.85 ± 1.18^a	19.71 ± 0.64^b	19.28 ± 0.36^b	16.43 ± 0.37^c
	creatinine (mg/dl)	2.18 ± 0.06^a	1.84 ± 0.03^b	1.80 ± 0.05^b	1.60 ± 0.03^c
	AST (IU/l)	50.86 ± 1.20^a	42.71 ± 1.15^b	42.28 ± 0.81^b	39.14 ± 0.83^c
	ALT (IU/l)	24.28 ± 1.49^c	33.71 ± 1.89^b	31.00 ± 1.72^b	38.86 ± 1.44^a
	ALP (IU/l)	158.71 ± 5.33^a	135.14 ± 4.26^b	137.57 ± 5.21^b	120.28 ± 4.77^c
	TP (g/dl)	8.13 ± 0.24^a	7.21 ± 0.12^b	7.13 ± 0.16^b	6.56 ± 0.15^c
	albumin (g/dl)	2.93 ± 0.11^b	3.21 ± 0.03^a	3.17 ± 0.04^a	3.23 ± 0.03^a
	globulin (g/dl)	5.20 ± 0.27^a	4.00 ± 0.11^b	3.95 ± 0.17^b	3.33 ± 0.16^c
	total bilirubin (mg/dl)	0.48 ± 0.07^a	0.43 ± 0.04^a	0.40 ± 0.05^a	0.41 ± 0.04^a

Means bearing same superscripts between columns do not differ significantly

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 II		Group III		Group IV	
	n	%	*n*	%	*n*	%
Salivation	Nil					
Vomition	6	85.71	4	57.14	3	42.86
Panting	6	85.71	2	28.57	2	28.57
Restlessness	7	100	4	57.14	3	42.86
Hyperpnoea	7	100	2	28.57	2	28.57
Defaecation	5	71.43	Nil	Nil	Nil	Nil
Urination	5	71.43	Nil	Nil	Nil	Nil

erythrocyte count (TEC) and lymphocyte count, and biochemical parameters such as 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 further decreased in the untreated control group animals whereas they 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 the combination of cloprostenol and cabergoline as compared to the bitches treated with either dinoprost tromethamine or cloprostenol alone. Before treatment the levels of haematological parameters like neutrophils and monocytes and biochemical parameters such as blood urea nitrogen (BUN), creatinine, aspartate transaminase, alkaline phosphatase, mean total protein and globulin were higher than the normal physiological value. These values increased further in the untreated control group of bitches whereas there was a significant decrease in these parameters in the treated group of bitches. A significant decrease was observed in the group of bitches treated with the combination of cloprostenol and cabergoline as compared to the bitches treated with either dinoprost tromethamine or cloprostenol alone. All the values of the above parameters are presented in Tables 1 and 2.

The bitches treated with dinoprost tromethamine showed a severe degree of side effects whereas in the other two groups, side effects were moderate. The side effects observed in each group are listed in Table 3. Recurrence rate was highest in the cloprostenol-treated group as compared to the other two groups. The bitches treated with the combination of cloprostenol and cabergoline showed the lowest recurrence rate. The percentages of post-treatment return to oestrus and conception rate was higher in the bitches treated with the combination of cloprostenol and cabergoline than in bitches treated with dinoprost tromethamine or cloprostenol alone. These values are presented in Table 4.

DISCUSSION

All the seven bitches were successfully treated using different treatment protocols resulting in 100% recovery rate in each group. Similar findings were reported by Sridevi et al. (2000) and Pande et al. (2004) who used Dinoprost tromethamine for treatment of canine pyometra. Tsumagari et al. (2005) reported that a normal blood picture was found in all the treated bitches immediately after completion of treatment using dinoprost tromethamine. Schepper et al. (1987) used natural $PGF_2\alpha$ for the treatment of pyometra at the dose rate of 250 µg/kg/day for five days and observed normal serum biochem-

Table 4. Post-treatment reproductive status

Parameters	Group II	Group III	Group IV
Recovered animals (*n*)	7	7	7
Recovery rate (%)	100.00	100.00	100.00
Animals came to estrus (*n*)	6 (85.71%)	2 (28.57%)	7 (100.00%)
Animals bred (*n*)	6 (85.71%)	2 (28.57%)	7 (100.00%)
Animals conceived (*n*)	4	1	5
Conception rate (%)	57.15	14.28	71.43
Bitches recurred (*n*)	3	6	2
Recurrence rate (%)	42.85	85.72	28.57

istry in all the treated bitches at the completion of treatment. Fieni (2006) and Khan et al. (2007) reported 84.4% and 83.33% recovery rates after using cloprostenol which was lower than in the present study. England et al. (2003) successfully treated bitches affected with pyometra using the combination of cloprostenol and cabergoline. Corrada et al. (2006) reported 83% recovery rate using a combination of cloprostenol and cabergoline for the treatment of pyometra. England et al. (2007) reported a normal blood haematological profile and normal serum biochemistry in all the treated bitches affected with pyometra after completion of treatment using a combination of cabergoline and cloprostenol.

Side effects have been shown to be dose-dependent and to diminish with repetition of treatment (Verstegen et al. 2008). Though salivation was the most common side effect observed after $PGF_2\alpha$ therapy (Pawde and Kumar, 1996; Pande et al. 2004; Smith 2006), in the present study this was not observed. This might be due to the administration of Atropine sulphate 10–15 min prior to the administration of $PGF_2\alpha$ (Lein et al. 1989). Attempts were made to minimise the side effects by withholding food and water to the bitches 4–6 h prior to the administration of $PGF_2\alpha$, using of Atropine sulphate and allowing the bitches a short walk after $PGF_2\alpha$ injection in order to facilitate early metabolism and excretion of the $PGF_2\alpha$ end product (Reddy et al. 2010). It was reported that $PGF_2\alpha$ has a direct action, whereas dopaminergic agonists act indirectly on the *corpus luteum* by blocking the luteotropic support provided by prolactin. The combination of these drugs thus permitted the use of lower $PGF_2\alpha$ doses, which reduced the side effects. Additionally, $PGF_2\alpha$ caused uterine contractions and promoted uterine evacuation contributing to treatment of the condition (England et al. 2003; Corrada et al. 2006).

The findings in the present study regarding recurrence rate and post-treatment reproductive status were in agreement with the reports of Verstegen et al. (2008), who reported that when the combination of cloprostenol and cabergoline was used serum progesterone concentrations declined in < 24 to 48 h where as low doses of prostaglandins alone exerted their effects only after three to four days. Cervical opening was generally observed after one day (or at most two days) with the combination protocol, versus several days when $PGF_2\alpha$ was used alone. As reported by Onclin et al. (1993) prolactin is the most important hormone regulating the corpora lutea of bitches and due to its luteotrophic property, repeated administration of prolactin inhibitors at a time more than 25 days after ovulation can result in a rapid and permanent reduction in plasma progesterone concentrations by causing substantial luteolysis in bitches. Clinical recovery after treatment of the bitches using a combination of cloprostenol and cabergoline might be due to synergistic effects of dopaminergic agonists and $PGF_2\alpha$ which potentiated the action of $PGF_2\alpha$ resulting in the induction of rapid luteolysis as reported by Corrada et al. (2006) and Verstegen et al. (2008). England et al. (2007) reported that the combination of a prolactin inhibitor and prostaglandin appeared to be effective in rapidly terminating the luteal phase and promoting uterine evacuation. This might be useful for conserving the future breeding capacity of bitches and in stabilising the pre-surgery condition of those bitches at a high anaesthetic risk.

The treatment of pyometra using natural $PGF_2\alpha$ (Dinoprost tromethamine) or synthetic $PGF_2\alpha$ (Cloprostenol) or a combination of a lower dose of synthetic $PGF_2\alpha$ (Cloprostenol) and cabergoline was found to be successful. Though lower doses of cloprostenol were effective in treating pyometra, these doses are not recommended because of the high rates of recurrence and lower conception rates. The treatment of canine pyometra using a combination of a dopamine agonist prolactin-inhibiting drug (Cabergoline) and a lower dose of synthetic $PGF_2\alpha$ (Cloprostenol) was found to be the most effective method among the three therapeutic protocols used in the present study.

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