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Medical management of canine cystic endometrial hyperplasia-pyometra with mifepristone, cloprostenol and cabergoline

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Abstract

Seven female dogs confirmed with CEH-P through history, clinical examination, ultrasonography and blood tests were selected for the study. Animals were treated with mifepristone (5 mg/kg BID PO on days 0, 1, 7 and every seven days until serum progesterone level was below 0.5 ng/mL), cloprostenol (1 µg/kg OD S/C for five consecutive days) and cabergoline (2.5 µg/kg OD PO for 12 days). The animals were evaluated using clinical, haematological, biochemical, B-mode and Doppler ultrasonographic parameters on days 0, 7, 14 and 21. The clinical signs, uterine diameter and haemato-biochemical parameters became normal by day 14 after the onset of treatment. By day 21 the serum progesterone concentrations decreased to below 0.5 ng/mL in all the animals. Animals showed a recovery time of 8.39 ± 1.54 days to regain appetite and 8.36 ± 1.45 days for cessation of vaginal discharge. All haematological and serological parameters returned to normal after medical treatment within 21 days of initiation of treatment, except VPRC, Hb and SDMA. Thus, a combination treatment with antiprogestin, antiprolactin and prostaglandin was found to be safe and effective in medical management of CEH-P with minimal side effects.

Keywords: *Cystic endometrial hyperplasia-pyometra, mifepristone, cabergoline, prostaglandin*

Cystic Endometrial Hyperplasia - Pyometra (CEH-P) is an inflammatory condition of the uterus marked by thickening of the endometrial lining and a bacterial infection that leads to pus accumulation in the uterine cavity. It is typically diagnosed within four months after oestrus (Hagman, 2018). Progesterone plays a role by inhibiting uterine contractions and promoting glandular activity in the endometrium, which creates an environment that favours the growth of opportunistic bacteria like *E. coli* (Gobello *et al.,* 2003). While medical treatment can be considered for young, valuable dogs that are intended for breeding, ovariohysterectomy (OHE) remains the preferred treatment option. Progesterone blockers are particularly noteworthy for treating pyometra in dogs, especially in cases of closed pyometra (Fieni, 2006). The combination of antiprogestins (aglepristone and mifepristone) with PGF2α has been reported to be highly effective (Fieni, 2006). However, aglepristone is highly expensive. There is also substantial literature on using aglepristone alone or with cloprostenol to treat open pyometra (Gobello *et al.,* 2003). Haematological evaluation throughout treatment could be

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a tool to assess the response and effectiveness of therapy in dogs with pyometra (Unnikrishnan *et al.,* 2020). Thus, this study investigated the effectiveness of progesterone receptor antagonists (mifepristone) combined with repeated low doses of prostaglandins and dopamine agonists for the medical management of CEH-P in dogs.

Materials and methods

Seven breeding female dogs with a history and clinical indications suggestive of CEH-P brought to the University Veterinary Hospital, Kokkalai were selected for the study. All the animals were subjected to thorough clinico-gynaecological, laboratory and ultrasonographic examinations to confirm the condition. Animals between 1-7 years of age, no previous history of treatment with progestins or oestrogens, leucocytosis (WBC > 18,000 cells/mL) and the presence of cystic endometrial hyperplasia with uterine luminal content on ultrasonography were included in the study.

All animals were treated with an antiprogestin, mifepristone (Mifegest 200 mg) per orally (PO) at the rate of 5 mg/kg body weight (BW) twice daily on days 0, 1, 7 and every seven days until serum progesterone level reached the basal value of less than 0.5 ng/mL, considering day 0 as the day of presentation of the dog (Simon, 2024). After initiation of vaginal discharge, cloprostenol (Clostenol® 250mcg/mL) was administered subcutaneously (SC) at the rate of 1 µg/kg BW OD for five consecutive days, starting from day 2. Amoxicillin-clavulanate (Tab. Petclav™) at the rate of 12.5 mg/kg BW bid PO enrofloxacin (Tab Ataxin) at the rate of 6 mg/kg BW PO OD was given for at least 14 days from Day 0 and other supportive therapies were given as per the clinical condition of the animal. Once the animal showed apparently normal appetite, cabergoline (CABERLIN®) was administered at the rate of 2.5 µg/kg OD PO mixed with food for 12 consecutive days (Simon,2024).

Blood sample was collected in EDTA and Serum vaccutainer tubes on days 0, 7, 14 and 21 of treatment. The samples were tested for total erythrocyte count (TEC), total leucocyte count (TLC), thrombocyte count, haemoglobin concentration (Hb), volume of packed red cells (VPRC) using automatic haematology analyser (Mythic 18 Vet, Switzerland), alkaline phosphatase (ALP), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine using semi-automatic biochemical analyser (Master T biochemistry analyser, Hospitex diagnostics, Italy), serum progesterone using automated chemiluminescence immunoassay analyzer (cobas® e 411, Roche Diagnostics, Germany), Symmetric dimethylarginine (SDMA) using the IDEXX Catalyst SDMA one test equipment and C-Reactive Protein (CRP) using canine sandwich enzyme-linked immunosorbent assay (ELISA).Clinical improvement was assessed by the average time required for patients to resume normal appetite, regain normal mentation and cessation of vaginal discharge. Statistical analysis was done using SPSS 24 software using repeated measures ANOVA.

Results and discussion

On the day of presentation, the mean physiological parameters, including rectal temperature, respiratory rate and pulse rate were within the normal range, although individual variations were noted. TEC (5.09 ± 0.22 $\times 10^6$/mm^3), VPRC (32.49 ± 2.12%) and Hb (11.93 ± 0.62%) concentrations were lower than the normal range on the days of presentation (Table 1). A significant increase ($p < 0.05$) in total erythrocyte count was observed from day 14 onwards and the value became 5.64 ± 0.24$\times 10^6$/mm^3 by day 21. Chinnu *et al.* (2017) also reported a lower TEC value of 4.68±0.27 on day 0. Reduced erythrocyte count in pyometra cases is attributed to decreased erythropoiesis due to toxic suppression of the bone marrow (Hardy and Osborne, 1974).TLC (31.47± 6.45$\times 10^6$/mm^3) and band cell (11.93 ± 0.62%) were elevated on the day of presentation indicating severe infection which gradually decreased on subsequent days of observation. Chinnu (2016) reported a drop in TLC from 24.25 ± 2.80$\times 10^6$/mm^3 to the normal range (14.45 ± 0.82$\times 10^6$/mm^3) 14 days after a combination treatment with cabergoline, mifepristone and cloprostenol. According to Kustritz (2005), leukocytosis could be the consequence of a generalised suppurative inflammation of the uterus in response to the infection and an aggressive bone marrow response brought on by elevated stress to the immune system. The medical approaches for the treatment of pyometra included reducing the impact of P4 (by either blocking its production or its activity), getting rid of the uterine infection, relaxing the cervix and drainage of the intraluminal pus to hasten the repair of the uterus (Hagman, 2018). There was a significant increase in

Table 1. Haematological parameters (Mean ± SE) in pyometra affected bitches on different days of observation (n= 7)

Variables	Day 0	Day 7	Day 14	Day 21	F-value (P-value)
Total erythrocyte count (10^6/mm^3)	5.09 ± 0.22	4.38 ± 0.51	4.67 ± 0.37	5.64 ± 0.24	3.458* (0.038)
Total leucocyte count (10^3/ mm^3)	31.47 ± 6.45	12.22 ± 2.5	10.74 ± 1.7	12.27 ± 1.36	7.806* (0.023)
Thrombocyte count (10^5/ mm^3)	275.57 ± 31.61	361.43 ± 34.47	304.57 ± 18.08	252.71 ± 11.77	3.363* (0.042)
Haemoglobin level (g/dL)	11.49 ± 0.66	10.10 ± 1.03	10.81 ± 0.9	11.39 ± 0.96	1.169^{ns} (0.349)
Band cells (%)	11.93 ± 0.62	3.10 ± 0.49	3.09 ± 0.38	2.21 ± 0.46	136.51** (<0.001)
Volume of packed red cells (%)	32.49 ± 2.12	28.49 ± 3.41	26.6 ± 2.56	26.81 ± 2.47	1.819^{ns} (0.180)

** Significant at 5per cent level; **Significant at 1per cent level; ns: non-significant*

thrombocyte count starting from day 7. Similar observations were reported by Unnikrishnan *et al.* (2020).

The mean CRP concentration was 136.18 ± 0.88 mg/L on day 0 which significantly reduced to 10.73 ± 0.23 mg/L by day 21 (Table 2). Acute-phase protein levels during inflammation revealed the degree of immune system activation (Dabrowski *et al.,* 2013). The reduction in CRP could be attributed to the effective elimination of infectious agents from the uterus. Hagman *et al.* (2006) stated that a reduction in CRP levels following treatment was associated with favourable clinical outcomes. The mean serum SDMA was 18.71 ± 5.45 on day 0 which became 14.86 ± 4.38 by day 21. As renal function declined the concentration of SDMA increased in its early stages, making it a reliable marker for the early detection of renal damage, as reported by Nabity *et al.* (2015). Andrade *et al.* (2023) reported a period of six months for renal biomarkers and clinical parameters to return to normal levels in CEH-pyometra. The mean initial serum P4 value was 13.31 ± 4.81 ng/mL which dropped to less than 0.5 ng/mL by day 21 in all animals. England *et al.* (2012) found a drop in serum P4 by day 3 following combined cabergoline-cloprostenol treatment. Verstegen *et al.* (2008) found that mifepristone, having a five-fold higher affinity for receptors than P4, mimicked the effects of luteolysis and caused cervical relaxation. Prolactin is known to support luteal function in female dogs, so the use of anti-prolactin agents led to a swift decrease in blood P4 levels (Antonov *et al.,* 2015). Administering $PGF_{2\alpha}$ leads to myometrial contraction and enhanced cervix relaxation, and after five days of diestrus, it exhibits luteolytic effects and decreases serum P4 levels (Gobello *et al.,* 2003). Hall (2012) observed that the luteolytic effects of cabergoline and cloprostenol were enhanced when used together, resulting in quicker luteolysis. The mean ALT concentrations were within normal physiological range on all days of observation suggesting reduced hepatocellular injury due to toxaemia in the present study.

On ultrasonography, the mean uterine horn diameter was 29.94 ± 1.63 mm on the day of presentation (Table 3). By day 21, uterine horn diameter (UHD) reduced to 6.74 ± 0.56 mm due to cervical relaxation induced by mifepristone, the spasmogenic and luteolytic effects of multiple cloprostenol injections and luteolysis caused by cabergoline's suppression on prolactin. The mean uterine wall thickness (UWT) reduced from 4.09 ± 1.25 mm (day 0) to 1.41 ± 0.34 mm by day 21. According to Bassessar *et al.* (2013), P4-induced endometrial and myometrial hyperplasia could be associated with an increased UWT. On Doppler sonography, the means of resistance index (RI) and pulsatility index (PI) were 0.63 ± 0.02 and 1.27 ± 0.1, respectively on day 0. The mean RI and PI values significantly increased to 0.78 ± 0.01 and 2.87 ± 0.08, respectively on day 21. As pyometra is an inflammatory disease, it leads to the local release of prostaglandin E and nitric oxide, which are strong vasodilators that enhance circulation (Pati *et al.,* 2021), causing an increased perfusion and a consequent reduction in RI and PI.

The mean peak systolic velocity (PSV) and end diastolic velocity (EDV) were 0.71± 0.02 and 0.28 ± 0.02 m/s, respectively on day 0, which significantly reduced to 0.40 ± 0.02 and 0.06 ± 0.02 m/s respectively by day 21. According to Rosa Filho *et al.* (2020), P4 induced a vasodilatory effect by reducing the concentration of calcium in vascular smooth muscle cells and by modulating the production of nitric oxide in blood vessels. Therefore, when antiprogestins or luteolytics were administered as part of medical treatment, they triggered progesterone receptor blockade, reduced inflammation and decreased uterine artery blood flow. The authors also added that the animals with pyometra undergoing therapy showed a gradual decrease in uterine vascularization as a positive response to effective treatment.

Clinical improvement was assessed by the average time required for patients to resume normal appetite, regain normal mentation and cessation of vaginal discharge. The mean duration (in days) taken for regaining appetite, normal mentation and cessation of vaginal discharge were 8.27 ± 1.54, 7.13 ± 1.27 and 8.36 ± 1.45, respectively. Increased vulvar discharge was observed between 24 to 48 hours, after the initial antiprogestin treatment according to Gobello *et al.* (2003). Antiprogestins indirectly caused cervical dilation and uterine contractions, which accelerated the emptying of

Table 2. Serological parameters in pyometra affected bitches on different days of observation (n= 7)

Variables	Day 0	Day 7	Day 14	Day 21	F-value (P-value)
CRP (mg/L)	132.27 ± 0.71	41.84 ± 0.76	11.89 ± 0.36	10.73 ± 0.23	12488.5** (<0.001)
BUN (mg/dL)	20.33 ± 3.48	14.80 ± 1.80	26.17 ± 13.14	24.66 ± 13.23	0.401^{ns} (0.565)
Creatinine (mg/dL)	1.38 ± 0.19	1.01 ± 0.19	0.99 ± 0.07	0.95 ± 0.06	2.919^{ns} (0.097)
ALP (IU/L)	254.2 ± 35.26	122.93 ± 22.96	111.64 ± 33.75	108.63 ± 11.75	0.945^{ns} (0.369)
ALT (IU/L)	27.65 ± 4.22	27.86 ± 4.06	23.20 ± 3.00	22.39 ± 3.12	2.477^{ns} (0.147)
SDMA (mcg/dL)	18.71 ± 5.45	18.29 ± 4.85	16.29 ± 4.81	14.86 ± 4.38	1.755^{ns} (0.230)
Serum Progesterone (ng/mL)	13.31 ± 4.81	5.06 ± 2.64	1.97 ± 0.38	0.44 ± 0.17	5.844* (0.046)

** Significant at 5per cent level; **Significant at 1per cent level; ns: non-significant*

the uterine cavity (Roland and France, 2005). Additionally, repeated administration of cabergoline resulted in a rapid and prolonged decrease in plasma progesterone levels, facilitating cervical opening and reducing uterine secretion (Onclin *et al.,* 1994). In dogs with pyometra, Verstegen *et al.* (2008) reported that vaginal discharge ceased 4–7 days after treatment with either cabergoline–$PGF_{2\alpha}$ or antiprogestin–$PGF_{2\alpha}$ combination, as prostaglandins exhibited a uterine spasmogenic function and also $PGF_{2\alpha}$ facilitated the evacuation of uterine fluid by reducing progesterone levels. This reduction led to further cervical relaxation and a decrease in uterine secretions. All the animals showed complete clinical cure by day 21 in the present study. According to Simon (2024), a combination of cabergoline and cloprostenol could induce a rapid clinical response when compared to cloprostenol alone in CEH-P. The author also suggested better conception rates (40-60%) and clinical cure rates (80-100%) with lower recurrence rates (10-40%) in medical management using a combination of mifepristone, cloprostenol and cabergoline.

Conclusion

In conclusion, the combined treatment of mifepristone, cabergoline and prostaglandin proved to be a safe and effective method for inducing cervical relaxation and managing CEH-P. This therapy counteracted the effects of progesterone by inducing luteolysis, enhancing uterine contractions to facilitate complete evacuation and promoting uterine regeneration. Additionally, it inhibited pathogens, indicated by improving leucocyte count and condition of animals over time. Given its proven effectiveness in improving conception rates, achieving clinical cures and reducing recurrence rates, this treatment is expected to yield better outcomes in subsequent oestrous cycles.

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