COMPARATIVE EFFICACY OF ANTIPROGESTIN AND DOPAMINE AGONIST IN THE TREATMENT OF CANINE PYOMETRA

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ABSTRACT

The study was designed to investigate the comparative efficacy of antiprogestin vis-à-vis dopamine agonist in the treatment of pyometra in bitches (n=16) presented to the Referral Veterinary Polyclinic - Teaching Veterinary Clinical Complex, Indian Veterinary Research Institute, Izatnagar. Pyometra was confirmed by presumptive clinical signs and transabdominal ultrasonography and the positive bitches were randomly subjected to two treatment regime, T1 (Mifepristone @ 2.5mg/kg p.o. on day 0, 1 and 10) and T2 (dopamine agonist, Cabergoline @ 5µg/kg, p.o. for 7 days), n=8/group. Cloprostenol @5µg/kg, s/c on alternate days for 7 days was included in both the groups along with empirical fluid and antibiotics. The treatment responses was determined by general clinical examination, changes of blood urea nitrogen, serum creatinine, prostaglandin F metabolites (PGFM) and progesterone (P4) level at pre-treatment and 10 days post-treatment. Recurrence or recovery was recorded on follow up examination and telephonic feedback after 100 days post treatment. A reduction in BUN and P4 concentration was recorded in both the treatment groups. The non-recurrence rate (%) of pyometra in the mifepristone treated bitches was 85.7 percent compared to 51.43 percent in cabergoline (P=0.09) treatment. From this study it can be concluded that addition of mifepristone improved the recovery rate with a reduction of recurrence rate in the medically treated pyometra cases in bitch.

Keywords: Pyometra, Mifepristone, PGFM, P4, Canine

INTRODUCTION

Pyometra is characterized as a hormone induced uterine bacterial infection and inflammation, leading to pus-filled uterus affecting intact middle aged and older bitches (Egenvall et al., 2001; Smith, 2006). Early diagnosis and rapid therapeutic intervention are necessary to prevent fatal outcome (Hardie, 1995). In open-cervix pyometra bitches are generally less systemically ill and often show no clinical signs other than vaginal discharge. In contrast, bitches with closed-cervix pyometra are usually very ill at presentation (Pretzer, 2008).

The most consistent clinical blood biochemistry finding includes elevated serum creatinine, blood urea nitrogen (Kuplulu et al., 2009) reflecting hepato-cellular damage in response to toxaemia, or diminished hepatic circulation due to dehydration. Ovario-hysterectomy remains the choice for pyometra treatment (Rootwelt-Andersen and Farstad, 2006), although has its own limitation when the risk of anaesthesia and course of surgery are life threatening with the toxaemic bitches (Fieni et al., 2014). Medical therapy is frequently resorted by owner due to surgical risks or to preserve breeding potential of the bitch. Combination of dopamine agonist, cabergoline and synthetic prostaglandin analogs, cloprostenol has been used successfully for management of pyometra (Gobello et al., 2003; Corrada et al., 2006; England et al., 2007). Antiprogestins are considered to be better than dopamine agonist as they directly block the action of progesterone (Verstegen et al., 2008). As a solitary agent, however, the antiprogestin is partially effective, as it does not have ecbolic effect. Mifepristone, administered as abortifacient and to treat progesterone dependent diseases in the women (Beal and Simmonds, 2002). However, Mifepristone has not been tested in bitches for the medical treatment of pyometra except one case study (Shah et al., 2016). Therefore, the study was done to investigate the efficacy of mifepristone vis-à-vis cabergoline in combination with cloprostenol in the treatment of pyometra.

MATERIAL AND METHODS

The study was carried out at Referral Veterinary Polyclinic – Teaching Veterinary Clinical Complex, Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India. A total of 16 bitches of different breeds such as Labrador, Spitz, Doberman, Pug, German Shepherd, St. Bernard and non-descript with presumptive symptoms of pyometra were included. About 75% bitches were nulliparous and 56.25% were at 7-10 years of age (Table 1). Confirmatory diagnosis of pyometra was done with

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trans-abdominal ultrasonography using a curvilinear probe of 3.5 MHz frequency based on the observation of uterine size, the thickness of uterine wall and the presence of anechoic fluid with echogenic particles accumulation within the lumen (Fig. 1).

Considering the breeding value, clinical status of the bitches, medical therapy was instituted consisting of two treatment regime viz., T1 (n=8), mifepristone per oral @ 2.5 mg/kg on day 0, 1 and 10 (Shah et al., 2016), while in T2 (n=8), cabergoline per oral @ 5 µg/kg once a day for 7 days (Noakes et al., 2009). Both the groups received 5 µg/kg cloprostenol s.c. on alternate days for 7 days. During the course of treatment, all the bitches were given empirical fluid therapy, supportive treatment with broad spectrum antibiotics, anti-histaminic and anti-emetic preparations.

Blood sample (5 mL) was collected from all the bitches at pre-treatment and 10 days post-treatment, serum was separated and stored at -20°C until estimation of blood urea nitrogen (BUN), creatinine, prostaglandin F metabolites (PGFM) and progesterone (P4) concentration. BUN and serum creatinine concentration were estimated using commercial kits validated for canine. Estimation of serum PGFM was done by competitive ELISA using commercial canine specific kit (Bluegene, China) and P4 concentration was estimated by radioimmunoassay using the solid phase I125 kit (Immunotech, France). The treatment responses were determined by clinical recovery, changes in serum biochemical concentration at 10 days post-treatment and recurrence rate based on follow up examination or telephonic feedback after 100 days post treatment.

Blood biochemical parameters at pre and post treatment period were compared using paired t test. The recurrence rates at 100 days post treatment in both the groups were compared by Kaplan-Meier survival analysis with Gehan-Breslow-Wilcoxon test. Significance was set at 95% level and Graphpad Prism 5.0 was used for construction of graphs.

RESULTS AND DISCUSSION

The principles governing the medical treatment of pyometra includes evacuating the uterine content, inhibiting the effects of P4, antimicrobial therapy to control infection and addressing dehydration (Verstegen et al., 2008). At diagnosis, bitches with pyometra had higher concentration of BUN, creatinine and PGFM compared to normal physiological values of healthy bitches as reported elsewhere (Hagman et al., 2006; Kuplulu et al., 2009). At post-treatment the serum concentration of BUN was reduced in both the treatment group, although the reduction was significant in T2 ($p<0.05$, Table 2). Similarly, a significant reduction in serum concentration of BUN observed at 10 days post treatment in T1 compared to T2, might be reflected with better recovery in mifepristone treatment. The serum concentration of creatinine was similar in pre-treatment and post treatment period in the bitches allocated to treatment with either T1 or T2 (Table 2). The persistent high level of creatinine for the period of 10 days post treatment might be due to the short time span of 10 days in between two sampling. The serum concentration of PGFM in the bitches with pyometra was reduced marginally in the post treatment period after treatment with T1 and the change was apparently more in T2 (Table 2). In the present study, majority of patient develop SIRS and considered for treatment. Hence, the very high level of PGFM at pretreatment period required longer time to reach into normal physiological range (Okano et al, 1998; Hagman et al., 2006).

The serum P4 concentration at pretreatment was significantly higher (3-fold) compared to post-treatment in the bitches subjected to T1 ($P<0.05$). However, in T2, although there was reduction in serum P4 concentration from pre-treatment to post-treatment but there was no statistical significance. The serum P4 concentration declined in both the treatment protocols and the effect of T1 was significant. The effect of antipogesterone, mifepristone proved to be more efficient in reducing serum P4 level, as it blocks the P4 receptors and give negative feedback effect, whereas the cabergoline acts indirectly by inhibiting the prolactin production. Our speculation is supported by the findings of Onclin et al. (1994), Hoffmann et al. (2001) and Wehrend et al. (2003).

The non-recurrence rate on day 100 post-treatment was 85.7 and 51.43 percent in T1 and T2, respectively. Gehan-Breslow-Wilcoxon test revealed that the survival curves were close to significance ($P=0.09$; Fig. 2). Treatment with mifepristone and cloprostenol controlled the clinical signs, improved the appetite and decreased the rate of recurrence till day 100 post-treatment. Our finding is well supported by the evidence where, mifepristone combined with cloprostenol was effective in controlling the clinical signs, and reduced the rate of recurrence till day 100 post-treatment in 91.11% bitches with pyometra (Shah et al., 2016). Analogs of PGF2a are commonly used by virtue of luteolytic and uterotonic effects. Dopamine agonists and antiprogesterone are used to counteract the effects of P4. Cabergoline with cloprostenol treatment was used as control as it significantly reduced the uterine diameter, alterations in

hematology and plasma progesterone by day 6-9 post-treatment in 95.5% bitches with open or closed pyometra and restored fertility in 33.3% of responded animals (England et al., 2007). From this result it is concluded that addition of mifepristone with cloprostenol improved the recovery rate with a reduction of recurrence rate in the medically treated pyometra cases in bitch.

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Table 1. Breed, age and parity wise distribution of pyometra cases

Attributes	No. of cases (%)
Breeds	
Labrador	5 (31.25)
Spitz	3 (18.75)
Non-descript	3 (18.75)
Doberman	2 (12.50)
German Shepherd	1 (6.25)
Pug	1 (6.25)
St. Bernard	1 (6.25)
Age (Years)	
≤ 3	3 (18.75)
>3 to ≤7	4 (25.0)
>7 to ≤10	8 (50.0)
>10	1 (6.25)
Parity	
Nulliparous	12 (75.0)
Parous	4 (25.0)

Table 3. Effect of treatment on serum biochemical parameters at pre and post treatment (mean ±SEM) in pyometra affected bitches

Serum biochemical		Pre treatment	Post treatment
	T1	26.1± 4.51†	19.56±2.58
BUN(mg/dL)	T2	30.63± 2.77	20.28±2.65*
Creatinine (mg/dL)	T1	1.13± 0.24	1.07± 0.25
	T2	0.88± 0.13	0.93± 0.16
PGFM (ng/mL)	T1	6.51± 1.21	5.72± 1.24
	T2	8.76± 2.2	6.27± 0.91
Progesterone (ng/mL)	T1	13.83± 3.54*	4.99±2.99
	T2	6.51± 1.31	3.89±1.64

Values with (*) indicates significant difference at $p<0.05$ and † indicate at $p<0.10$