

Evaluation of Novel Therapeutic Approach and Surgical Management of Closed Cervix Pyometra in Bitches

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ABSTRACT

The present study was conducted in the twenty-eight number of bitches aged between 2 to 6 years presented to SAC-OP-OG unit of Madras Veterinary College Teaching Hospital with a history of inappetence, lethargy, polyuria, polydipsia and distended abdomen which was further confirmed as pyometra by radiography and ultrasound examination. Further, the bitches were divided equally into group I and II. Group I (n=14) was treated with Tab. Mifepristone @ 2.5 mg/kg b.wt. per OS, Tab. Cabergoline @ 5 µg/kg b.wt. per OS and Tab. Misoprostol @ 100 µg per vaginum for 7 to 14 days. Group II (n=14) bitches directly underwent ovariohysterectomy. The assessment of uterine distention was performed by follow-up ultrasonography on day 7, 14, 21 and 28. The blood samples were collected on day 0 (before administering treatment) and on day 7, 14 and 21 in both groups for haemato-biochemical examination. In Group I, 78.57% and 63.63% of cases responded and conceived, respectively, in next cycle, while 9.09% cases had recurrence of pyometra. The altered haemato-biochemical indices in Group I and II were reversed between 14 to 21 and 7 to 10 days, respectively. The study concluded that the physiological and haemato-biochemical reversal is delayed in Group I with ovariohysterectomy, but mifepristone and cabergoline used in Group I prove to be safe and efficient therapeutic protocol for management of closed pyometra and restoring the breeding ability in young bitches.

Key words: Bitch, Cabergoline, Cloprosternol, Closed cervix pyometra, Mifepristone, Misoprostol.

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INTRODUCTION

Canine pyometra is a dioestrus disorder in intact bitches mainly affecting bitches over 8 years of age characterized by the accumulation of pus in the uterus due to primary hormonal imbalance that facilitates bacterial adherence, colonisation, and growth with or without persistent corpus luteum (Fieni *et al.*, 2014). Other terms to describe canine pyometra in relation to pathogenesis like chronic endometritis, chronic purulent metritis, cystic endometrial hyperplasia (CEH) or cystic endometrial hyperplasia - pyometra complex etc. has also been coined (Hagman, 2018). In cases of open cervix pyometra, the cervix is more or less open and the uterine horns are distended with purulent fluid, resulting in significant vulvar discharge (Lika *et al.*, 2011). Vulvar discharge may be mucoid, purulent, sanguine-purulent or haemorrhagic. In some cases, the cervix remains closed (closed cervix pyometra), with no vulvar discharge, but the accumulation of purulent fluid distends the lumen of the uterus, and in late evolution, the endometrium is generally atrophied. Closed cervix pyometra is particularly fatal, which needs early recognition, diagnosis and treatment to avoid disastrous results like death due to septicaemia and toxæmia (Gupta *et al.*, 2019).

The conventional treatment for canine pyometra is ovariohysterectomy (Lika *et al.*, 2011) which is curative and preventive for the recurrence of pyometra (Fieni *et al.*, 2014). However, surgery is always associated with the risk of anaesthesia, and peritonitis and renders the bitch sterile.

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During the last two decades, numerous therapeutic protocols have been proposed to treat open cervix pyometra in bitches but, conservative medical treatment of pyometra, provided by prostaglandins, is not recommended in closed cervix pyometra which can cause uterine rupture, peritonitis, severe renal failure, or a significant electrolyte imbalance (Gogny and Fieni, 2016). Hence, this study was designed to assess the efficacy of progesterone blocker in combination with

dopamine agonist therapy in the case of young bitches with closed cervix pyometra.

MATERIALS AND METHODS

Location and Animal Selection

This study was conducted in bitches presented to Madras Veterinary College Teaching Hospital, Madras Veterinary College, Chennai at Gynaecology and Obstetrics, Small Animal Outpatient Unit. The twenty-eight number of bitches aged between 2-6 years with the history of inappetence, lethargy, polyuria, polydipsia and distended abdomen, and gynaecological, ultrasonographical (Fig. 1) and radiographical (Fig. 2) examination confirmed closed cervix pyometra were selected for our experiment.

Experimental Design

Twenty-eight bitches were randomly divided into two groups, viz., Group I and Group II each comprised of 14 bitches. Group I was treated with Tab. Mifepristone @ 2.5 mg/kg b.wt. per OS, Tab. Cabergoline @ 5 µg/kg b.wt. per OS for seven days and Tab. Misoprostol @ 100 µg per vaginum (after 48 h of the first dose of Tab. Mifepristone and Cabergoline) for four consecutive days. Group II was subjected to Ovariohysterectomy as per the standard protocol (Fig. 3).

Bitches of both group were treated with antibiotics (Inj. Vetclox @ 20 mg/kg b.wt. and Inj. Metronidazole 15 mg/kg b.wt.), fluid therapy (inj. RL @ 10 mL/kg b.wt.) and supportive therapy (Inj. Pantaprazole @ 1 mg/kg b.wt. and Inj. Tribivet @ 0.1 mL/kg b.wt.) daily for 14 days.

Group I bitches were subjected to ultrasonographical examinations on day 7, 14, 21 and 28 after initiation of treatment to assess the efficacy of medical therapy. Haemato-biochemical parameters were assessed on days 0, 7, 14 and 21 in both groups. Animals of both groups were kept under observation to assess their speedy recovery. Group I bitches were observed for the onset of next estrus, conception and any recurrence of pyometra. The accumulated data were analysed statistically by IBM® SPSS® software.

RESULTS AND DISCUSSION

Efficacy of Medical Therapy

In group I bitches, the vaginal discharge started on day 3 from the initiation of treatment as brown colour thin bloody discharge. Further, the nature of discharge was changed to thick mucopurulent on day 7 and on day 14 discharge was serous in nature, which was unnoticed by day 21 (Fig. 4a,b,c,d). These findings were in close agreement with observations of Thangamani *et al.* (2018). Fieni *et al.* (2014)



Fig. 1: Ultrasonographical examination revealing Multiple anechoic uterine sacculations

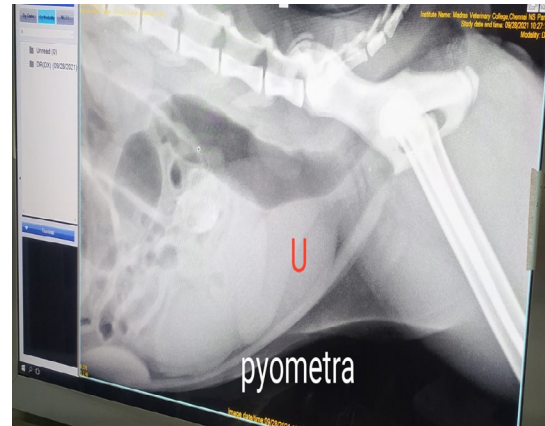


Fig. 2: Radiographical examination revealing an enlarged uterus and displacement of intestines



Fig. 3: Surgical procedure of ovariohysterectomy with closed cervix pyometra (Group II)



suggested that the opening of the cervix induces evacuating a large volume of purulent discharge in bitches with closed cervix pyometra which leads to an immediate improvement in general condition and appetite.

On ultrasonographical examination, the mean diameter of uterine sacculations of the closed cervix pyometra in group I bitches was reduced significantly ($p < 0.05$) from day 7, 14, 21 (Fig. 5 a,b,c,d) and 30 as compared to day 0. The mean endometrial thickness was also gradually reduced numerically from day 7, 14 and 30, as compared to day 0, which indicates the normal restoration of endometrial thickness initiated after the treatment and restored on day 14 after medical management (Table 1).

Table 1: Assessment of uterine sacculations and endometrial thickness during different days in medical management of closed cervix pyometra (Group I)

Days	Anechoic sacculations diameter (cm)	Changes in endometrial thickness (cm)
Day 0	3.81±0.46 ^a	0.49±0.04
Day 7	2.01±0.32 ^a	0.34±0.56
Day 14	0.66±0.08 ^b	0.28±0.01
Day 21	0.41±0.47 ^b	0.22±0.13
Day 30	0.11±0.06 ^b	0.24±0.02

Values with different superscripts within the column differ significantly $p < 0.05$.

The reduction in diameter of uterine sacculations was positively correlated with the quantity of vaginal discharge and recovery in canine pyometra in group I bitches, which concurred with the finding of Versteegen *et al.* (2008) and Hagman (2018), who reported that the evacuation of the uterus leads to the reduction in the size of anechoic sacculations in the bitches affected from pyometra. Similarly, the reduced thickness of the uterine wall and reduction in serum biochemical parameters of the present study concurred with Manokaran *et al.* (2018), who reported the decrease in serum biochemistry values indicating restoration of the endometrial thickness.

In group I, out of 14 bitches, 11 bitches had responded (78.57 %, 11/14) to medical therapy and exhibited the signs of estrus in the subsequent cycle (2-6 months depending on the breed of bitches) and were advised for mating. Out of 11 bitches, 63.63 % (7/11) were conceived and the pregnancy was confirmed ultrasonographically on day 40 post-mating. On the other hand, 9.09 % (1/11) of group I bitches underwent recurrence of pyometra in the subsequent cycle (7 months later), which was subjected to ovariohysterectomy.

These findings coincided with Fieni *et al.* (2018), who found that medical management with antiprogesterins, *i.e.* aglepristone alone and in combination with dopamine agonist, cabergoline was most effective in the management



Fig. 4: Nature of vaginal discharge after medical management in closed cervix pyometra bitches (Group I)



Fig. 5: Ultrasonographical examination on different days in medical management of closed cervix pyometra bitches (Group I)

of closed cervix pyometra with 76.66% and 66.66% bitches responded and conceived, respectively, in the subsequent cycle. The recurrence of pyometra and conception rate in the present study was similar to the observations (68.2% and 9%) of Melandri *et al.* (2019) in the bitches treated with antiprogestins.

General Health and Haemato-Biochemical Profile

In the present study, mean haemoglobin concentration was 10.66 ± 0.71 and 9.9 ± 1.1 g/dL in group I and II bitches, respectively, which was below the normal level (12-18.9 g/dL) which indicates that the closed cervix pyometra is associated with anaemia which is in agreement with the several workers (Jena *et al.*, 2013; Fieni *et al.*, 2014; Thangamani *et al.*, 2018). This might be due to loss of red blood cells by diapedesis into the uterine lumen apart from depressed feed intake and impaired erythropoiesis under the toxæmic condition in

severely affected cases (Jena *et al.*, 2013). Haemoglobin level was increased significantly ($p < 0.05$) following treatment and rebound to the normal range on day 14 in group I and on day 7 in group II bitches, respectively (Table 2). This finding is in agreement with Lika *et al.* (2011) who reported faster recovery in bitches, who underwent surgical intervention because surgical management eradicated the source of infection and toxicity.

Before treatment, the mean PCV percentage was 22.375 ± 1.77 and 24.39 ± 1.13 % in group I and II bitches, respectively, which was below the normal level range (35-57%). In the group, I and II bitches post-treatment PCV percentage was increased significantly ($p < 0.05$) and it rebound to the normal range on day 7 and 14 (Table 2). In the present study before treatment, the mean PCV level was decreased in the bitches affected with pyometra indicating a mild normocytic, normochromic and regenerative type of

Table 2: Haematological values in canine closed cervix pyometra on different days of medical (Group I) and surgical (Group II) treatment

Days	Mean Hb (g/dl)		Mean PCV (%)		Mean TEC(x10 ⁶ /μL)		Mean TLC(x10 ³ /μL)	
	Gr. I	Gr. II	Gr. I	Gr. II	Gr. I	Gr. II	Gr. I	Gr. II
0	10.66±0.71 ^{aA}	9.9±1.1 ^{aA}	22.375±1.77 ^{aA}	24.39±1.13 ^{aB}	3.42±0.39 ^{aA}	2.73±0.67 ^{aB}	23.76±1.23 ^{aA}	24.87±3.03 ^{aA}
7	11.89±1.75 ^{aA}	13.3±0.68 ^{bB}	29±1.45 ^{bA}	39.4±0.76 ^{bB}	3.9±1.15 ^{bA}	5.3±0.36 ^{bB}	14.58±1.12 ^{bA}	12.9±1.77 ^{bB}
14	12.63±0.9 ^{bA}	12.9±2.65 ^{bA}	39.63±0.11 ^{cA}	42.98±2.65 ^{cA}	4.5±0.36 ^{cA}	6.9±0.02 ^{cB}	10.87±0.15 ^{cA}	8.5±0.43 ^{cB}
21	13.51±0.26 ^{bA}	14.11±1.53 ^{bA}	41.51±0.23 ^{cA}	47.97±1.53 ^{dB}	5.3±2.16 ^{dA}	7.22±0.03 ^{dB}	08.11±1.14 ^{dA}	6.4±0.27 ^{dB}

Values with different superscripts within the column (a,b,c,d) and within the row (A,B) differ significantly (p<0.05).

anaemia. This was found to concur with Dabhi and Dhami (2006) and Shah *et al.* (2017), who reported decreased PCV level in the bitches due to high level of toxins production in closed cervix pyometra that causes severe dehydration and polyurea which in turn leads to decrease in PCV level. In this study, the gradual increase of PCV in group I bitches and fast recovery in group II bitches observed was in agreement with Lika *et al.* (2011), who recorded that the recovery of PCV in the bitches underwent surgical management was immediate due to the excision of the source of infection and toxins which causes dehydration, and Fieni *et al.* (2014) suggested the slow increase in PCV in medically treated bitches because the evacuation of uterine content and infection was gradual.

In pyometric bitches mean TEC (x10⁶/μL) values before treatment were 3.42±0.39 and 2.73±0.67 x10⁶/μL in group I and II bitches, respectively, which indicates below the normal level (4.95-7.87 x10⁶/μL). It then increased and found in the normal range on day 7 in group II, and raised gradually in group I and found to be in normal range on day 21 (Table 2). The mean total erythrocyte count before treatment was decreased in the bitches affected with pyometra indicating anaemia (Jena *et al.*, 2013; Shah *et al.*, 2017). Anaemia might be associated with the toxic depression of the bone marrow whereas severe non-regenerative, microcytic, hypochromic anaemia accompanied by extremely high white blood cell levels might be indicative of a concurrent blood loss (Thangamani *et al.*, 2018). Present finding is in agreement with Unnikrishnan *et al.* (2018), who reported a gradual increase in TEC because of the short life of circulating erythrocytes due to the effect of toxins, on the other hand ovariohysterectomy eradicated the source of toxins which resulted in faster recovery in TEC.

Leucocytosis was noticed on day 0 in group I and II bitches with TLC 23.76±1.23 and 24.87±3.03 x10³/μL, respectively, indicating the existence of inflammatory process. Similarly, higher values of TLC have been reported in previous studies by Patil *et al.* (2013), Lakshmikanth *et al.* (2016), Shah *et al.*

(2016) and Samantha *et al.* (2018), which was due to an aggressive bone marrow response to combat the infection. In the present study, the TLC decreased to normal level in medically treated group bitches on day 14 which concurred with the findings of England *et al.* (2007) in bitches treated with cloprostenol and cabergoline. Renukaradhy (2011) reported a decrease in TLC by day 9 after antiprogesterin-PGF_{2α} combination treatment. Chinnu (2016) reported a decrease in TLC by 14 days after treatment with mifepristone and cloprostenol in the combination of cabergoline. In this study, the combined action of mifepristone, cabergoline and misoprostol caused early luteolysis, cervical relaxation and uterine contraction, resulting in better drainage of uterine contents. Once the source of stimulation of the immune system is removed, a return to normal leucogram occurs. On the other hand, Fieni *et al.* (2014) mentioned that TLC showed reversal within normal range by day 7 in the bitches which underwent ovariohysterectomy due to the removal of the source of infection.

In the present study, BUN and creatinine were found elevated in the bitches affected with pyometra (Table 3). On day 0, the mean BUN level was 123.35±2.03 and 137.12±1.05 mg/dL and the mean creatinine level was 5.43±0.59 and 4.7±0.64 mg/dL in group I and II, respectively, which was in agreement with Jitpen *et al.* (2014) and Sharma *et al.* (2020). Increased levels of BUN and creatinine indicate the hampered efficiency of kidneys to remove nitrogenous waste from the circulation and renal dysfunction as a result of endotoxemia, glomerular dysfunction and renal tubular damage. In our study, the mean BUN and creatinine in serum reversal to the normal level on day 21 and 14 in the medically treated group. On the other hand, for surgically managed bitches, the levels of mean BUN and creatinine were found to be in the normal range on day 14 and 7. The decrease in BUN and creatinine level coincided with Haji *et al.* (2018), who reported decrease in BUN and creatinine by day 18 and 12 in the cases of canine pyometra treated with cloprostenol and mifepristone.

Table 3: Biochemical values in canine closed cervix pyometra on different days of medical (Group I) and surgical (Group II) treatment

Days	BUN (mg/dL)		Creatinine (mg/dL)	
	Group I	Group II	Group I	Group II
0	123.35±2.03 ^{aA}	137.12±1.05 ^{aA}	5.43±0.59 ^{aA}	4.7±0.64 ^{aA}
7	87.75±15.1 ^{bA}	49.89±1.99 ^{bB}	3.56±1.76 ^{aA}	1.425±0.14 ^{bB}
14	40.92±2.98 ^{cA}	27.21±0.19 ^{cB}	1.54±0.45 ^{bA}	0.88±0.332 ^{bA}
21	23.22±0.21 ^{dA}	17.08±1.54 ^{dA}	0.76±0.86 ^{bA}	0.45±0.44 ^{bA}

Values with different superscripts within the column (a, b, c) and within the row (A, B) differ significantly (p<0.05).



CONCLUSION

It can be concluded from this study that the physiological and haemato-biochemical reversal in therapeutic management of pyometra in bitches was gradual in comparison to ovariectomy. However, surgery is associated with the risk of anaesthesia and renders the bitch sterile. Administration of mifepristone along with cabergoline and misoprostol was found to be the safer and more efficient drug for management of closed cervix pyometra and restoring the breeding ability in bitches. So, medical management with mifepristone along with cabergoline and misoprostol should be considered as the novel approach to treating closed cervix pyometra as the first choice of treatment in young bitches without cystic endometrial hyperplasia.

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