



Haemato-biochemical changes in mis-mated pregnant dogs treated for termination of pregnancy[#]

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Abstract

Study was conducted to compare the efficacy of mifepristone alone or in combination with cabergoline for termination of unwanted pregnancy in different stages of gestation in dogs by haemato-biochemical evaluation. Twenty-four pregnant dogs with a history of misalliance were divided into two groups: Group I consisting of dogs between 30 and 35 days of gestation, and Group II with dogs over 35 days of gestation. Each group was further divided into two subgroups: subgroup a, which was treated with mifepristone alone, and subgroup b, which received both mifepristone and cabergoline. Haemato-biochemical parameters were studied on the day of presentation, day 6 and day 11. On haematology, no significant difference was observed in TEC, Hb, VPRC, platelet count, MCV, MCH and MCHC between the days of observation within and between groups. The dogs, on different observation days, exhibited a mean total TLC at the upper limit of the normal range. On day 6, mean TLC increased in Group I and decreased in Group II. Serum BUN, creatinine and ALP levels were within normal range on all days of observations, there was no significant difference between the days of observation within and between the groups. Decline in ALP levels over time in all dogs, suggesting that a portion of ALP production by fetuses. Based on haemato-biochemical analysis on different days of observation, treatments using mifepristone alone or in combination with cabergoline was found to be effective in termination of pregnancy during mid gestation and after mid gestation.

Keywords: Mifepristone, dog, haematology, biochemical, mismating

Mis-mating is a frequent issue in canine veterinary practice, often occurring because dog owners are unaware of the oestrus status of their female dogs. Termination of unwanted pregnancy is one of the most frequent reproductive requests from dog owners. Progesterone secretion during the whole gestational period is necessary for the maintenance of pregnancy in bitch. In dogs, the corpus luteum is the sole source of progesterone, as the canine placenta does not naturally synthesize significant amounts of the hormone.

Medical termination of unwanted pregnancies is an alternative to surgical intervention when the owner does not want to compromise the animal's future fertility and it helped to avoid surgical risks and postoperative complications

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(Jyothi *et al.*, 2019). Riou *et al.* (2001) reported that progesterone receptor antagonists competed with progesterone for uterine receptors which can lead to insufficient uterine stimulation, causing foetal death and subsequent expulsion or resorption. Dopamine agonists are effective for termination of pregnancy if given after 30 days of pregnancy, before 30 days permanent luteolysis was not achieved (Post *et al.*, 1988; Concannon and Meyers-Wallen, 1991).

The aim of the present study was to assess the haematological and biochemical alterations in dogs treated for medical termination of pregnancy (MTP) during and after mid gestation using mifepristone alone or in combination with cabergoline.

Materials and methods

The study was carried out in mis-mated dogs, presented to University Veterinary Hospital, Kokkalai and Teaching Veterinary Clinical Complex, Mannuthy. A total of 24 dogs brought with the history of misalliance, diagnosed as pregnant by ultrasonography and presented for MTP with written consent of pet owners were included in the study.

Dogs scheduled for MTP were divided into two groups of 12 dogs each, based on gestational age as determined by trans-abdominal ultrasonography as Group I and Group II. Group I consisted of dogs with a gestational age of 30-35 days, while Group II comprised of dogs with a gestational age of greater than 35 days. Each group was then randomly divided into subgroups a and b, with a minimum of six dogs.

In group Ia, dogs were administered with mifepristone (Mifegest 200mg) @ 2.5 mg/kg body weight twice daily per orally (PO) for five days. In group Ib, dogs were administered with mifepristone @ 2.5 mg/kg body weight twice daily along with cabergoline (Cabgoline 0.25 mg) @ 5 µg/kg body weight once daily PO for five days. In group IIa, dogs were administered with mifepristone @ 2.5 mg/kg body weight twice daily PO for five days. In group IIb, dogs were administered with mifepristone @ 2.5 mg/kg body weight twice daily along with cabergoline @ 5 µg/kg body weight once daily PO for five days.

Whole blood and serum samples were collected and subjected to haematological and serum biochemical studies on Day 1, 6 and 11 of treatment. Haematological parameters like total leukocyte count ($10^3/\mu\text{L}$), total erythrocyte count ($10^6/\mu\text{L}$), haemoglobin concentration (g/dL), volume of packed red cells (%), platelet count ($10^3/\mu\text{L}$) mean corpuscular volume (fL), mean corpuscular haemoglobin (pg) and mean corpuscular haemoglobin concentration (g/dL) were assessed using automatic haematology analyser (Mythic 18 Vet, Woodley, Switzerland) immediately after collection.

Serum biochemical parameters like blood urea nitrogen (mg/dL), creatinine (mg/dL) and alkaline phosphatase (IU/L) were directly measured by spectrophotometry immediately after serum separation using semi-automated biochemistry analyser (Alpha Chem 100, Alpha technologies, Chennai). The statistical analysis was done using SPSS version 24 and the test used was repeated measures ANOVA.

Results and discussion

On day 6, number of dogs responded to the treatment in various groups were as follows: 1/6 in Group Ia, 3/6 in Group Ib, 6/6 in Group IIa and 5/6 in Group IIb. On day 11, all dogs responded to treatment except one in Group Ia. The results of haemato-biochemical evaluation in different groups are shown below:

Total leukocyte count (TLC)

Mean TLC ($10^6/\mu\text{L}$) of Group Ia, Group Ib, Group IIa and Group IIb dogs in the study on various days of observation are presented in Table 1. The mean TLC on different days of observation in the different groups were near the threshold value. The normal TLC in dogs ranged between 5.0 - $14.1 \times 10^3/\mu\text{L}$ (Aiello *et al.*, 2016). In group Ib, a significant increase was obtained on day 6 ($p < 0.05$) when compared to day 1 and day 11. In group IIa, a significant decrease was obtained in day 6 ($p < 0.05$). On day 6, significant increase in TLC observed in group Ib compared to other groups ($p < 0.05$). There was a significant increase observed in Group I and a significant decrease observed in Group II in mean TLC on day 6.

The dogs, on different observation days, exhibited a mean total TLC near the upper limit of the normal range. According to Dimco *et al.* (2013), the circulating levels of leucocytes in pregnant animals are high. This increase can be attributed to several factors, including high oestrogen secretion, elevated plasma cortisol levels or the maternal immune system's response to the foetal allograft (Awodu *et al.*, 2002). Both mifepristone and cabergoline work synergistically to disrupt the hormonal balance which might amplify the immune system activation, leading to a spike in TLC in group Ib. According to Frehner *et al.* (2018), the lymphocytosis observed indicated an active immune response associated with luteolysis, a critical process of pregnancy termination in dogs.

In the dogs terminated at 30-35 days of gestation, mean TLC increased on day 6, while in the dogs over 35 days of pregnancy, a decrease in mean TLC was observed in the present study. The increase in TLC in dogs at 30-35 days could be due to a stronger inflammatory response as foetal tissue breakdown and expulsion triggered immune system. In contrast, dogs beyond 35 days may experience a more advanced stage of foetal development with a less intense inflammatory response, possibly because the body handles the expulsion of more developed tissues

with reduced immune activation or inflammation (Pereira *et al.*, 2023). Holst *et al.* (2019) reported a decreased leukocytic activity during later part of luteal phase in non-pregnant dogs.

Ozalp *et al.* (2013) reported that administering aglepristone to rabbits did not alter the lymphocyte levels significantly, but caused a notable increase in neutrophil counts. Gunzel-Apel *et al.* (2009) also reported an increase of TLC after medical induction of abortion in dogs. Georgiev *et al.* (2010) suggested that this might be associated with local inflammation caused by the abortion process or stress related to foetal expulsion. However, Binli *et al.* (2022) reported normal TLC after treatment with aglepristone.

Table 1. Total leukocyte count (Mean \pm SE) of mis-mated on different days of MTP (n=24), $10^3/\mu\text{L}$

Groups (n=6)	Total leukocyte count		
	Day 1	Day 6	Day 11
G Ia	12.24 \pm 1.50	14.84 ^{AB} \pm 1.73	14.60 \pm 1.67
G Ib	16.81 ^a \pm 1.84	20.06 ^{ba} \pm 3.14	15.97 ^a \pm 3.20
G IIa	16.81 ^a \pm 1.40	12.37 ^{bb} \pm 1.25	11.67 ^b \pm 0.64
G IIb	13.23 \pm 0.85	12.59 ^B \pm 0.33	11.62 \pm 0.74

Means bearing different lower-case letters in a row differ significantly ($p < 0.05$)

Means bearing different upper-case letters in a column differ significantly ($p < 0.05$)

Total erythrocyte count (TEC)

Mean TEC of different groups in the study on various days of observation are presented in Table 2. Mean TEC in all the days of observation in the study groups were within normal range. The normal TEC in dogs ranged 4.95 to 7.87 $\times 10^6/\mu\text{L}$ (Aiello *et al.*, 2016). Ozalp *et al.* (2013) and Binli *et al.* (2022) found that aglepristone administration did not alter TEC. The reduction in TEC in pregnant dogs is attributed to increased plasma volume in order to meet the increased metabolic demands of the fetuses and subsequent haemodilution (Ayana *et al.*, 2024), along with the shortened lifespan of erythrocytes

Table 2. Total erythrocyte count (Mean \pm SE) of mis-mated dogs on different days of MTP (n=24), $10^6/\mu\text{L}$

Groups (n=6)	Total erythrocyte count		
	Day 1	Day 6	Day 11
G Ia	5.40 \pm 0.34	5.04 \pm 0.30	5.17 \pm 0.33
G Ib	5.22 \pm 0.26	5.25 \pm 0.24	5.40 \pm 0.25
G IIa	5.57 \pm 0.80	5.78 \pm 0.79	6.13 \pm 0.81
G IIb	5.13 \pm 0.41	4.92 \pm 0.41	5.32 \pm 0.30

Values within a row and column did not differ significantly ($p > 0.05$)

during pregnancy. The results indicated that the dose and frequency of abortifacients did not cause evident bone marrow suppression.

Haemoglobin concentration (Hb)

Mean Hb (g/dL) in different groups in the study on various days of observation are presented in Table 3. There was no significant difference ($p > 0.05$) in mean Hb between the days of observation within and between the groups. Ozalp *et al.* (2013) and Binli *et al.* (2022) found that aglepristone administration did not result in significant alterations in haemoglobin concentration. The mean Hb at the lower limit of the normal range is attributed to increased plasma volume and haemodilution leading to slight anaemia during pregnancy in dogs which is physiological due to disproportion between erythrocyte volume and the gestation induced increased plasmatic volume (Verstegen-Onclin and Verstegen, 2008).

Volume of packed red cells (VPRC)

The mean VPRC recorded in different groups in the study on various days of observation are presented in Table 3. Mean VPRC in the all the days of observation in different groups were below and near the lower limit of normal range. The normal VPRC in dogs ranged of 35-57 per cent (Aiello *et al.*, 2016). There was no significant difference ($p > 0.05$) in mean VPRC between the days of observation within and between the groups.

Ozalp *et al.* (2013) and Binli *et al.* (2022) found that aglepristone administration did not result in significant alterations in VPRC levels. The mean VPRC below the normal range in the present study is attributed to increased

Table 3. Haemoglobin concentration (g/dL) and Volume of packed red cells (%) of mis-mated dogs on different days of MTP (n=24)

Groups (n=6)	Haemoglobin concentration (g/dL)			Volume of packed red cells (%)		
	Day 1	Day 6	Day 11	Day 1	Day 6	Day 11
G Ia	13.93 \pm 0.93	13.10 \pm 0.84	13.43 \pm 0.83	36.23 \pm 2.67	34.00 \pm 2.21	35.70 \pm 2.41
G Ib	12.87 \pm 0.62	13.05 \pm 0.45	13.62 \pm 0.61	36.23 \pm 1.71	36.42 \pm 1.01	37.35 \pm 1.92
G IIa	12.45 \pm 1.10	12.82 \pm 1.30	13.70 \pm 1.35	36.53 \pm 3.12	36.08 \pm 3.34	38.10 \pm 3.95
G IIb	11.60 \pm 0.59	11.00 \pm 0.70	12.27 \pm 0.41	32.58 \pm 2.41	31.15 \pm 2.32	33.47 \pm 1.57

Values within a row and column did not differ significantly ($p > 0.05$)

plasma volume leading to slight anaemia during pregnancy in dogs (Concannon and Hansel, 1977).

Platelet count (PC)

Mean PC ($10^3/\mu\text{L}$) in different groups in the study on various days of observation are presented in Table 4. Mean PC on all days of observation in the study groups were within normal range. The normal PC in dog ranged $211 - 621 \times 10^3/\mu\text{L}$ (Aiello *et al.*, 2016). There was no significant difference ($p>0.05$) in mean PC between the days of observation within and between the groups. The results suggested that the treatments did not cause significant alterations in platelet production (Binli *et al.*, 2022).

Table 4. Platelet count (Mean \pm SE) of mis-mated dogs on different days of MTP (n=24), $10^3/\mu\text{L}$

Groups (n=6)	Platelet count		
	Day 1	Day 6	Day 11
G Ia	285.33 \pm 15.37	341.5 \pm 22.70	323.83 \pm 34.99
G Ib	324.83 \pm 62.65	440.5 \pm 82.01	416.33 \pm 91.53
G IIa	261.83 \pm 70.18	267.5 \pm 77.88	286.5 \pm 51.63
G IIb	304.83 \pm 30.49	355 \pm 35.12	391.67 \pm 25.50

Values within a row and column did not differ significantly ($p>0.05$)

Mean corpuscular volume (MCV)

Mean MCV (fL) of different groups in the study on various days of observation are presented in Table 5. Mean MCV on all the days of observation in study groups were within the normal range with no significant difference recorded. The drugs and protocols used in the study

did not cause any disruptions in erythropoiesis or lead to conditions such as anaemia or macrocytosis, where RBCs might become abnormally small or large (Binli *et al.*, 2022).

Mean corpuscular haemoglobin (MCH)

Mean MCH (pg) of different groups in the study on various days of observation are presented in Table 5. The mean MCH concentrations on different days of observations in the study groups were in normal range. There was significant difference in mean MCH ($p<0.05$) in between groups Ia and IIa on the day 6. According to Dimco *et al.* (2013) and, there were no significant changes in MCH during pregnancy in dogs. The drugs and protocols in the present study did not induce stress on red blood cells in terms of their haemoglobin content and that overall red blood cell function, in terms of oxygen transport capacity, was unaffected by the protocols (Binli *et al.*, 2022).

Mean corpuscular haemoglobin concentration (MCHC)

Mean MCHC (g/dL) of different groups in the study on various days of observation are presented in Table 5. There was no significant difference ($p>0.05$) in mean MCHC between the days of observation within and between the groups. There were no significant changes in MCHC during pregnancy in dogs (Dimco *et al.*, 2013; Binli *et al.*, 2022).

Blood urea nitrogen (BUN)

Mean BUN (mg/dL) of different groups in the study on various days of observation are presented in Table 6. There was no significant difference ($p>0.05$) in mean BUN levels between the days of observation within and between the groups. This was in accordance with Eren and Yenilmez (2019) and Binli *et al.* (2022). Normal BUN levels in the treated dogs indicated that the drugs and/or protocols used had no evident effect on the renal function.

Table 5. Mean corpuscular volume (fL), mean corpuscular haemoglobin (pg) and mean corpuscular haemoglobin concentration (g/dL) of mis-mated dogs on different days of MTP (n=24)

Groups (n=6)	MCV (fL)				MCH (pg)		MCHC (g/dL)		
	Day 1	Day 6	Day 1	Day 6	Day 11	Day 11	Day 1	Day 6	Day 11
G Ia	66.97 \pm 0.91	66.16 \pm 1.34	25.87 \pm 0.6	26.00 ^A \pm 0.55	25.62 \pm 0.65	68.67 \pm 1.76	34.58 \pm 0.94	35.83 \pm 0.93	34.32 \pm 0.83
G Ib	68.75 \pm 0.91	67.9 \pm 0.73	24.47 \pm 0.51	24.65 ^{AB} \pm 0.63	24.73 \pm 0.57	68.62 \pm 0.36	35.10 \pm 0.42	34.40 \pm 2.04	36.05 \pm 0.70
G IIa	66.37 \pm 3.25	64.83 \pm 3.54	22.88 \pm 1.37	23.08 ^B \pm 1.19	23.37 \pm 1.21	65.45 \pm 3.38	34.55 \pm 0.60	35.92 \pm 0.87	35.60 \pm 0.75
G IIb	67.35 \pm 2.77	68.2 \pm 3.44	24.18 \pm 1.31	23.80 ^{AB} \pm 1.13	23.63 \pm 0.72	67.45 \pm 2.32	35.93 \pm 1.19	34.98 \pm 1.31	35.23 \pm 0.39

Means bearing different upper-case letters in a column differ significantly ($p<0.05$)

Serum creatinine

Mean serum creatinine (mg/dL) of different groups on various days of observation are presented in Table 6. There was no significant difference ($p>0.05$) in mean serum creatinine levels between the days of observation within and between the groups. This was in accordance with Eren and Yenilmez (2019) and Binli *et al.* (2022). The normal creatinine levels indicated that the renal system or nephrons were not damaged by the metabolites of the drugs used in the study.

Alkaline phosphatase (ALP)

Mean ALP (mg/dL) of different groups in the study on various days of observation are presented in Table 7. Mean serum ALP level on different days of observations were within the normal range except on Day 1 of Group IIb. The normal serum ALP in dog ranged 1–114 IU/L (Aiello *et al.*, 2016). High levels of ALP were observed in Group II as compared to Group I. All the four groups demonstrated a decreasing trend in ALP levels over time. There was highly significant difference ($p<0.01$) in mean ALP levels in group IIb on different days of observations.

In pregnant and post-parturient dogs, there was a gradual increase in total serum ALP activity from conception to weaning, though ALP levels remain within the reference intervals (Fernandez and Kidney, 2007). Increase in ALP during later stages of pregnancy was resulted from hepatic haematogenesis in canine fetuses (Kimura and Kotani, 2018). The decrease in ALP after MTP is in accordance with Binli *et al.* (2022). In the present study, the decrease in ALP after MTP indicated that the serum ALP level in pregnant dogs is also contributed by foetal liver. The increased amount of ALP in the advanced stage might be due to increased production from growing foetus.

Higher efficacy with least duration for completion of pregnancy termination and minor side-effects was shown by dogs treated after mid-gestation with mifepristone. The combination therapy of mifepristone and cabergoline during mid-gestation had more advantages over mifepristone alone but this scenario was not observed after mid-gestation protocols.

Table 7. Alkaline phosphatase (ALP) (Mean \pm SE) of mis-mated dogs on different days of MTP (n=24), IU/L

Groups (n=6)	Serum alkaline phosphatase		
	Day 1	Day 6	Day 11
G Ia	85.74 ^{AB} \pm 16.67	69.54 \pm 14.44	56.91 \pm 11.74
G Ib	92.19 ^{AB} \pm 31.75	82.03 \pm 17.34	62.88 \pm 12.36
G IIa	100.92 ^A \pm 15.78	74.82 \pm 15.09	63.35 \pm 17.02
G IIb	170.02 ^{aB} \pm 24.43	115.1 ^b \pm 28.81	76.43 ^c \pm 24.60

Means bearing different lower-case letters in a row differ significantly ($p<0.05$)

Means bearing different upper-case letters in a column differ significantly ($p<0.05$)

Conclusion

It was concluded that the use of mifepristone alone or in combination with cabergoline during and after mid-gestation for terminating unwanted pregnancy in dogs did not adversely affect the haematological and biochemical values. The statistical changes observed in various parameters are individual fluctuations within normal limits and are due to the normal physiological effects of pregnancy. Definite variations were observed only in TLC and serum ALP levels following medical termination of unwanted pregnancy in dogs.

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Conflict of interest

The authors declare no conflicts of interest.

Table 6. Blood urea nitrogen and serum creatinine of mis-mated dogs on different days of MTP (n=24), mg/dL

Groups (n=6)	Serum creatinine (mg/dL)			BUN (mg/dL)		
	Day 1	Day 6	Day 11	Day 1	Day 6	Day 11
G Ia	0.99 \pm 0.08	0.91 \pm 0.10	0.95 \pm 0.05	18.24 \pm 1.71	16.06 \pm 2.24	14.31 \pm 1.41
G Ib	1.04 \pm 0.16	0.86 \pm 0.10	1.01 \pm 0.12	16.70 \pm 2.10	17.08 \pm 2.12	18.45 \pm 1.70
G IIa	0.96 \pm 0.03	1.05 \pm 0.03	1.04 \pm 0.03	20.92 \pm 2.48	16.68 \pm 0.73	16.09 \pm 0.65
G IIb	0.97 \pm 0.16	0.84 \pm 0.10	0.90 \pm 0.07	15.80 \pm 1.74	17.79 \pm 2.01	15.83 \pm 0.60

Values within a row and column did not differ significantly ($p>0.05$)

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