RESEARCH ARTICLE

Impact of Different Therapies on Haematological Parameters and Therapeutic Outcome in Subclinical Endometritic Buffaloes

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Abstract

The objective of this study was to compare the effect of administration of intrauterine dextrose, s/c levamisol and intrauterine $PGF_2\alpha$ on haematological indices and therapeutic response in endometritic buffaloes. Twenty eight repeat breeder buffaloes with subclinical endometritis were randomly assigned into four groups. Seven animals were kept as Control (untreated C), and the rests were assigned to three treatment group, *i.e.,* T1 (Dextrose I/Ut, 50 mL 4 times on the day of estrus), T2 (Levamisol s/c, @ 2.5 mg/kg b.wt. on day 0, 7 and 14 of the cycle), and T3 ($PGF_2\alpha$ I/Ut, @ 0.25 mg in 0.5 mL saline twice, on the day of first and next estrus). Following treatment the values of Hb, TEC and PCV elevated significantly and TLC values dropped to normal or near normal in all three treatment groups as compared to control group. Furthermore, the post-treatment neutrophils and lymphocytes counts were elevated significantly in all four groups. However, there was no any definite pattern of eosinophils and basophils. The therapeutic response (clinical recovery) was 14.29, 71.43, 85.71 and 42.86 % in T0, T1, T2 and T3 group, respectively. The corresponding conception rates were 0.00, 60.00, 66.67 and 66.67 %. The results conclude that, Dextrose intrauterine, Levamisol s/c, and $PGF_2\alpha$ intrauterine can be used effectively to manage subclinical endometrtitis in buffaloes.

Key words: Buffalo, Dextrose, Endometritis, Levamisole, $PGF_2\alpha$

Ind J Vet Sci and Biotech (2023): 10.48165/ijvsbt.19.5.12

Introduction

Subclinical endometriris and non-specific genital infections are one of the most common causes of repeat breeding syndrome in buffaloes (Samatha and Ramesh, 2013). Clinical endometritis is defined as purulent uterine discharge detectable in vagina of cattle 21 days or more postpartum or a mucopurulent discharge detectable in vagina after 26 days postpartum, while subclinical endometritis is characterized by lack of clinical signs of endometritis (Sheldon *et al.,* 2006). Furthermore, subclinical endometritis is an important cause of infertility and is often undiagnosed (Dutt *et al.,* 2017), hence goes untreated and have substantial impact on herd's fertility. Moreover, subclinical endometritis results in subfertility even after successful resolution of the disease. Diagnosis of the condition is often made by transrectal palpation and ultrasonography of the reproductive tract (Kasimanickam *et al.,* 2004), evaluation of vaginal mucus to define an inflammatory discharge through vaginoscopy, the Metricheck tool (Le Blanc *et al.,* 2002) and more accurately by cytobrush, lavage, or biopsy technique (Kasimanickam *et al.,* 2004; Lee *et al.,* 2018).

Endometritis is occasionally self-limiting with recovery occurring after subsequent estrous cycles. If uterine defense mechanism (UDM) is compromised, bacteria may colonize the uterus and lead to the development of uterine infection and endometritis. Thus, the ideal therapy for uterine infections is to eliminate bacteria from the uterus without compromising UDM and no adulteration of milk or meat. Various drugs, *viz.,* antimicrobials (Makki *et al*., 2017), non-antibiotics (Ahmadi *et al*., 2019; Parikh *et al*., 2022), hormones (Sheldon *et al*., 2004; Butani *et al.,* 2009; Kumar *et al*., 2010) and immunomodulators (Parikh *et al*., 2022; Singh *et al*., 2023) have been

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How to cite this article: Verma, S. K., Kumar, R., Singh, B., Srivastava, S., & Verma, R. K. (2023). Impact of Different Therapies on Haematological Parameters and Therapeutic Outcome in Subclinical Endometritic Buffaloes. Ind J Vet Sci and Biotech. 19(5), 60-64.

Source of support: Nil

Conflict of interest: None

Submitted: 18/05/2023 **Accepted:** 28/07/2023 **Published:** 10/09/2023

tested to manage uterine infections with varying success. Available reports suggest that levamisol can be used to resolving the endometritis and as alternative or adjunct to antibiotic therapy (Singh *et al.,* 2017). Intrauterine dextrose solution has been used with varying degree of success to manage subclinical endometritis in cattle (Makki *et al.,* 2017; Ahmadi *et al.,* 2019), but it has been never tried in endometritic buffaloes. The hypothesis of present study was that intrauterine dextrose, $PGF_2\alpha$ and parenteral Levamisol would improve subclinical endometritis induced changes in haematological indices and augment reproductive outcomes of such buffaloes.

Materials and Methods

The study was carried out on repeat breeder buffaloes following approval from Institutional Animal Ethics Committee (No. IAEC/CVSc/P-09/2022). The cases presented at Veterinary Clinical Complex, College of Veterinary Science, ANDUAT, Kumarganj, Ayodhya and State Veterinary Hospitals in adjoining areas of Kumarganj (India) were included in the study. Twenty eight repeat breeder buffaloes with subclinical endometritis were selected on the basis of history and breeding records, per-rectal examination and physico-chemical characteristics of cervico-vaginal mucus at estrus (appearance and consistency, White side test, pH), and randomly divided in to 4 equal groups, *viz*., Group T0 (no treatment); T1 (intrauterine dextrose, 50 mL as slow I/Ut infusion, repeated 4 times until 200 mL was used, on day of estrus), T2 (Levamisole @ 2.5 mg/kg body weight, s/c, on 0, 7^{th} and 14^{th} day of the cycle) and Group T3 (PGF2α; Dinoprost, two doses 21 days apart intrauterine; first at commencement of experiment, second at subsequent estrus; 0.25 mg in 0.5 mL normal saline).

Approximately 10 mL blood was collected aseptically in clean sterile EDTA vial by jugular vein puncture. Each animal was sampled twice, at start of treatment (S1) and at subsequent estrus after treatment (S2) and haematology was done immediately. At subsequent standing estrus following treatment all the buffaloes were inseminated twice, 12 h apart. Pregnancy was confirmed per-rectally at 45-60 days after last insemination. Data were presented as mean ± SE and analyzed by using completely randomized design and Duncan's NMRT for effect of groups, and paired 't' test for effect of periods at significance of $p<0.05$ (Snedecor and Cochran, 1994).

Results and Discussion

Effect of Treatment Protocols on Haematological Indices

The mean (±SE) values of haemoglobin (Hb), PCV, TEC and TLC recorded on start of treatment and at subsequent estrus post-treatment in different groups of endometritic buffaloes are depicted in Table 1.

At pre-treatment sampling the Hb, PCV, TEC and TLC values did not differ significantly among groups; but the corresponding post-treatment values of Hb, PCV and TEC were significantly ($p<0.05$) increased and TLC values were significantly decreased as compared to those of pre-treatment values and of control group of repeat breeder buffaloes; however significant decline in PCV values was noted in control group too. At subsequent estrus following treatment, the mean Hb and TEC concentrations were highest in dextrose treated buffaloes followed by levamisole and $PGF_2\alpha$ treated groups, and the mean PCV level was highest in levamisole treated buffaloes followed by dextrose and $PGF_2\alpha$ treated groups, while the mean TLC concentration was lowest in dextrose treated buffaloes followed by $PGF_2\alpha$ and levamisole treated groups. The observations suggest that these treatment protocols have a positive impact on Hb, PCV, TEC and TLC concentration, which might be due to overall improvement in uterine health and elimination of bacterial infection *in-utero*.

Like present observations many previous studies reported lower Hb, PCV, TEC and higher TLC values in repeat breeder cattle (Perumal *et al.,* 2013; Heidarpour *et al.,* 2014) and buffaloes (Patil *et al.,* 2015; Singh *et al.,* 2023) as compared to cyclic fertile animals. The findings indicate positive impact of therapeutic protocols on subclinical endometritis induced changes in haematological parameters. All of the therapeutic regimens effectively cleared infection from the uterus, which may have contributed to the buffaloes' improved overall health. To the best of our knowledge, intrauterine infusion of dextrose and $PGF_2\alpha$ has been never tested in subclinical endometritic buffaloes; so we could not compare our results.

The increment in the Hb, PCV, TEC and drop in TLC values in the blood samples of endometritic buffaloes after treatment with hypertonic dextrose solution might be due to elimination of bacterial infection from the uterus that improved general body condition of the animal. Similar observations were also recorded in endometritic buffaloes with uterine lavage with physiological saline (Singh *et al.,* 2023). Similar trends in haematological parameters were also recorded in levamisole treated endometritic buffaloes (Singh *et al.,* 2023), which may have been caused by the drug's stimulation of cell-mediated immune reactivity by accelerating T-lymphocyte differentiation, increasing sensitivity to mitogens and antigens, and increasing phagocyte activity. As a result, the uterine microbial burden decreased, which improved the animal's overall physical health. The stimulation of myometrial contraction and the phagocytic activity of uterine polymorphonuclear cells may be responsible for the considerable increase in haemoglobin concentration in the blood samples of endometritic buffaloes treated with intrauterine infusion of PGF2α.

The decreased packed cell volume for endometritic buffaloes observed in current study may be related to anaemic alterations brought on by the infection and variations in haemo-concentrations. As they are necessary

for proper health and productivity, an ideal value of haemoglobin and packed cell volume are needed for efficient oxygen transport. According to Thrall (2004), inflammatory cytokines decreased erythropoietin, which in turn causes a decrease in erythropoiesis and, ultimately, a decrease in blood cell volume. Infections of the genital tract may result in higher TLC values in endometritic buffaloes for greater need of cellular defence at the infection site (Kekan *et al.,* 2005).

Effect of Treatment Protocols on Differential Leucocytes Counts (DLC)

The mean (±SE) values of DLC recorded before and after treatment in different groups of endometritic buffaloes are depicted in Table 2.

At pre-treatment sampling the DLCs values did not differ significantly among different treatment groups of repeat breeding buffaloes. At post-treatment stage, *i.e.* at subsequent estrus, the lymphocyte count significantly ($p<0.01$) increased and neutrophil count decreased in all groups over their pre-treatment values and also of control group. Moreover, significant period effect was noted only in monocyte count in group C; eosinophil count in groups C and T1, and in basophil count in groups T2 and T3. Thus all of the therapeutic regimens effectively cleared infection from the uterus. To the best of our knowledge, intrauterine infusion of hypertonic dextrose solution and PGF2α is never used for treatment of repeat breeder buffaloes with subclinical endometritis, so we could not compare our results.

The changes in neutrophil and lymphocyte counts are comparable with the report of Singh *et al.* (2023), who also recorded significant ($p<0.05$) decline in neutrophil and increment in lymphocyte values following uterine lavage with normal saline solution, parenteral levamisole and PGF2α therapy in endometritic buffaloes. Similar to present observations lower lymphocyte count was recorded in endometritic cattle (Ahmad *et al.,* 2003) and buffaloes (Singh *et al.,* 2023) as compared to cyclic animals. Conversely, Perumal *et al.* (2013) found repeat breeder cows to have a higher lymphocyte count than typical cyclic fertile cows.

Leukocytes, notably neutrophils, increased significantly in bacterial infections. Blood leukocytes are phagocytic, mobile cells that are impacted by a variety of inflammatory and pathological diseases. Value variations depend on a number of variables, including the infection's intensity, the causative agent's characteristics, the animal's resistance, and the location of the inflammatory response. For the reproductive tract's innate immunity, or non-specific immunity, leukocytes are involved. At various stages of the estrous cycle and pregnancy, the intermittent influx of WBCs from the blood into the uterus and their subsequent return may induce a minor deviation in the WBCs count. Infection in the genital tract may be the cause of the lower lymphocyte count in the endometritic repeat breeding buffaloes (Kekan *et al.,* 2005). The lymphopaenia seen in the current study may be a relative lymphopaenia brought on by neutrophilia

Table 1: Mean (±SE) Haemoglobin, PCV, TEC and TLC values in different groups of buffaloes before and after treatment

	Hb (g/dL)		PCV (%)		TEC ($x10^6$/µL)		TLC ($x10^3$/µL)	
Group	**Pre-treatment**	**Post- treatment**	**Pre-treatment**	**Post- treatment**	**Pre-treatment**	**Post- treatment**	**Pre-treatment**	**Post- treatment**
C (Untreated)	10.20 ± 0.12^{a}	10.40 ± 0.13^{a}	32.08 ± 0.47^{a}	$31.29\pm0.52^{a**}$	6.15 ± 0.09^{ab}	6.11 ± 0.09^{a}	18.13 ± 0.36^{a}	17.97 ± 0.40^{c}
T1 (Dex)	10.70 ± 0.24^{a}	$13.16\pm0.20^{c**}$	31.62 ± 0.20^{a}	$36.53\pm0.65^{b**}$	6.05 ± 0.18^{b}	$8.97\pm0.56^{b**}$	17.95 ± 0.42^{a}	$9.23\pm0.45^{a**}$
T2 (Lev)	10.23 ± 0.57^{a}	$11.89\pm0.41^{b*}$	31.73 ± 0.16^{a}	$36.65\pm1.79^{b*}$	5.81 ± 0.38^{a}	$8.07\pm0.57^{b*}$	17.77 ± 0.38^{a}	$10.64\pm0.24^{ab**}$
T3 (PG)	10.36 ± 0.30^{a}	$11.24\pm0.24^{b**}$	31.74 ± 0.14^{a}	$33.20\pm0.15^{ab**}$	5.40 ± 0.11^{a}	$6.43\pm0.08^{a**}$	17.99 ± 0.41^{a}	$10.94\pm0.32^{b**}$
P value	0.6637	0.0001	0.6891	0.0032	0.1226	0.0001	0.9274	0.0001

*P<0.05, **P<0.01 between periods; Means bearing common superscript within the column do not differ significantly (P>0.05).

Table 2: Mean (±SE) DLC count (%) in different groups of buffaloes before and after treatment

	Neutrophil (%)		Lymphocyte (%)		Monocyte (%)		Eosinophil (%)		Basophil (%)	
Group	**Pre-treatment**	**Post- treat-ment**	**Pre-treat-ment**	**Post- treat-ment**	**Pre-treat-ment**	**Post- treat-ment**	**Pre-treat-ment**	**Post- treat-ment**	**Pre-treat-ment**	**Post- treat-ment**
C (Untreated)	48.36 ± 0.18^{a}	$48.19\pm0.20^{b*}$	43.50 ± 0.15^{b}	$44.54\pm0.19^{a**}$	3.29 ± 0.06	$3.38\pm0.06^{**}$	4.08 ± 0.19	$3.99\pm0.18^{*}$	1.27 ± 0.05^{a}	1.30 ± 0.06^{a}
T1 (Dex)	48.41 ± 0.12^{a}	$42.48\pm0.16^{a**}$	44.02 ± 0.43^{b}	$47.22\pm0.37^{b**}$	3.43 ± 0.14	3.52 ± 0.10	4.45 ± 0.17	$4.30\pm0.16^{*}$	1.38 ± 0.10^{a}	1.42 ± 0.11^{ab}
T2 (Lev)	47.39 ± 0.41^{a}	$43.34\pm0.59^{a**}$	43.75 ± 0.42^{ab}	$47.35\pm0.39^{b**}$	3.43 ± 0.11	3.60 ± 0.08	4.37 ± 0.16	4.31 ± 0.17	1.34 ± 0.03^{a}	$1.23\pm0.04^{a**}$
T3 (PG)	47.49 ± 0.16^{a}	$42.70\pm0.18^{a**}$	42.92 ± 0.34^{a}	$47.21\pm0.21^{b**}$	3.50 ± 0.11	3.52 ± 0.11	4.56 ± 0.16	4.56 ± 0.12	1.38 ± 0.09^{a}	$1.44\pm0.10^{b*}$
P value	0.0149	0.0001	0.0149	0.0001	0.5986	0.4061	0.1812	0.0969	0.5028	0.0238

*P<0.05, **P<0.01 between periods; Means bearing common superscript within the column do not differ significantly (P>0.05).

and/or lymphocyte extravasation to the site of infection or inflammation. Lymphocytes are critical for immunity. B-lymphocytes produce IgG-dominant antibodies. Both the humoral antibody response and cell-mediated immunity depend heavily on lymphocytes.

The increase in the lymphocyte and drop in neutrophil count of blood samples of endometritic buffaloes after treatment with dextrose intrauterine might be due to inhibition of bacterial growth locally by reducing water activity, increasing uterine tone or by nurturing endometrial cells (Brick *et al.,* 2012). Levamisole treatment resulted in a significant increase in the lymphocyte count in blood samples from endometritic buffaloes, which may have been caused by the drug's stimulation of cell-mediated immune reactivity by accelerating T-lymphocyte differentiation, increasing sensitivity to mitogens and antigens, and increasing phagocyte activity. As a result, the uterine microbial burden decreased, which improved the animal's overall physical health. Present observation in levamisole treated buffaloes compared well with Singh *et al.* (2023), who also recorded significant increase in lymphocyte count following levamisole treatment in endometritic buffaloes. The significant increase in the lymphocyte count following intrauterine infusion of PGF2α might be due to stimulation of myometrial contraction that expelled debris and microorganisms from contaminated and phagocytic activity of uterine polymorphonuclear cells. No citation was available in the literature regarding effect of intrauterine infusion of dinoprost on lymphocyte count of blood samples in endometritic buffaloes.

According to Kekan *et al*. (2005), the variation in monocytes and eosinophil count seen in repeat breeding endometritic buffaloes may be caused by genital tract infection. The largest form of leukocytes is called monocytes. Before becoming macrophages or dendritic cells and entering the tissues, these immune cells circulate in the blood for several days. Monocytes offer defence against infections caused by bacteria, fungi, viruses, and protozoa. These cells enhance immune responses, consume foreign substances, eliminate dead cells, and kill bacteria. Eosinophil defends our body from many pathogens, primarily parasites and bacteria. They develop in the bone marrow before being discharged into the circulation. The present findings are consistent with the results of Ahmad *et al*. (2003) and Reddy *et al.* (2012), who found lower eosinophil count in endometritic cows and buffaloes than typical cyclic fertile animals, while Perumal *et al.* (2013) found higher eosinophil level in recurrent breeder cows than typical cyclic fertile cows. A similar trend of non-significant change in eosinophil count was also recorded by others (Reddy *et al.,* 2012; Dash *et al.,* 2019; Singh *et al.,* 2023) following treatment of endometritic cows and buffaloes with uterine lavage, levamisole and $PGF_2\alpha$.

Similar to our observations, Singh *et al.* (2023) also did not record any significant change in basophil count following treatment of endometritic buffaloes. In addition to causing inflammatory reactions during immunological responses, basophils also have a role in the development of both acute and chronic allergic disorders, such as hay fever, asthma, atopic dermatitis, and anaphylaxis. They have the ability to phagocytose (consume cells), create the inflammatory chemicals histamine and serotonin, as well as the blood thinning agent heparin.

Therapeutic Response of Different Treatment

The therapeutic response in terms of clear mucus discharge negative for Whites side and other tests was 14.29, 71.43, 85.71 and 42.86 % in T0, T1, T2 and T3 respectively. The corresponding conception rates were 0.00, 60.00, 66.67 and 66.67 %. The results conclude that, intrauterine dextrose, Levamisol s/c and $PGF_2\alpha$ i/ut can be used effectively to manage subclinical endometrtitis in buffaloes. Similarly, few previous studies reported improved reproductive performace of endometritic cattle subjected with intrauterine dextrose (Brick *et al.,* 2012; Maquivar *et al.,* 2015), parenteral levamisole (Singh *et al.,* 2023) and intrauterine PGF2α (Lopez-Gatius *et al.,* 2004).

Conclusions

The findings of the present study revealed that subclinical endometritis induces alterations in normal haematological parameters. Intrauterine infusion of dextrose (50x4=200 mL) or $PGF_2\alpha$ (0.25 mg in 0.5 mL saline) during estrus and levamisol s/c (@ 2.5 mg/kg on day 0, 7 and 14 of the cycle) could mitigate these changes and improved clinical recovery and conception rate in subclinical endometritis buffaloes, hence these treatment protocols can be recommended to manage the repeat breeder buffaloes with subclinical endometritis.

Acknowledgement

The facilities provided by the Dean, College of Veterinary Science & AH, Kumarganj, Ayodha, are gratefully acknowledged.

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