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Comparative Efficacy of Antibiotics and PGF2α in the Treatment of Postpartum Endometritis in Nili-Ravi Buffaloes

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ABSTRACT

This study compared the effects of ceftiofur HCL, oxytetracycline, and PGF2α on controlling postpartum endometritis and improving reproductive performance in Nili Ravi buffaloes. Sixty-two buffaloes with clinical endometritis were divided into five treatment groups. Group 1 (n=12) received intrauterine oxytetracycline; Group 2 (n=12) received oxytetracycline and PGF2α; Group 3 (n=12) received ceftiofur HCL; Group 4 (n=15) received ceftiofur HCL and PGF2α; and Group 5 (n=11) was the untreated control. Treatment success rates were 75%, 83.33%, 67.33%, 73.33%, and 45.5% in the respective groups. The control group had a significantly lower success rate ($P \leq 0.05$). Days to first service were lowest in Group 2 (71.66±16.35). Days open were also significantly lower in Group 2 (106.75±14.66). First and second service conception rates were highest in Group 2 (58.33% and 83.33%). Services per pregnancy were lowest in Group 2 (1.8±0.74). Overall, Group 2 (oxytetracycline + PGF2α) showed better reproductive outcomes compared to the control. The study concluded that oxytetracycline combined with PGF2α improves postpartum reproductive performance in buffaloes.

INTRODUCTION

Buffaloes (Bubalus bubalis) play an important role in farmer's economy as a source of milk, meat and skin. Clinical endometritis (CE) is a common disorder of lactating buffaloes that negatively affects reproductive performance and is defined as the inflammation of the endometrial lining of the uterus Characterized clinically by mucopurrulent or purulent vaginal discharge Occurring 21 to 40 days after parturition (Brick et al. 2012;Gilbert et al. 2005; LeBlanc et al. 2002a). However, Sheldon et al. (2006) proposed defining puerperal metritis as an inflammation of the uterus that results in fetid red-brown watery vaginal discharge (VD), fever (>39.5°C), and signs of systemic illness such as decreased milk yield, dullness, or other signs of toxemia. Approximately 80–100% of the cows have uterine contamination with bacterial agents in the first 2

weeks postpartum (LeBlanc 2008). Three to 4 weeks after parturition ,the number and variety of bacterial species diminish substantially in healthy cows (LeBlanc 2008).But some species of bacteria, such as Trueperella pyogenes, Escherichia coli, Streptococcus spp., Fusobacterium spp., and Prevotella melaninogenica, can cause a purulent vaginal discharge(Bondurant 1999;Williams et al. 2005). Clinical Endometritis is associated with ovarian failure (Sheldon et al.2009), poor reproductive performance, increased culling rate because of reproductive failure (LeBlanc et al. 2002b), and reduced milk yield (Dubuc et al. 2011a). Hence, treatment of endometritis is very important in management of reproduction in dairy herd .A wide variety of therapies for endometritis has been reported, including systemically or locally administered antibiotics, or systemically injected PGF2α (LeBlanc2008). Intrauterine infusion of antimicrobial agents can cause high concentration of antibiotic in the uterine lumen which is the location of the infection (Gilbert and Schwark 1992; Gustafsson 1984). .Oxytetracycline is one of the most widely used antibiotics in treatment of Clinical Endometritis by veterinarians in dairy farms, but antibiotic residues will be found in milk for some time after intrauterine treatment (Makki et al.2016; Tan e t al.2007). Oxytetracycline intrauterine administration represents a useful therapy, especially in treatment and prophylaxis of postpartum endometritis in cows (Chaudhery et al., 1987; Khan and Khan, 1989; Singh et al., 2001; Malinowsk et al., 2004). The direct intrauterine administration of Oxytetracycline produces immediate therapeutic concentrations in caruncles and endometrium of both healthy and affected animals (Roncada et al., 2000; Bateman et al., 2002; Shams–Esfandabadi et al., 2004; Kaczmarowski et al., 2004) and because of its relatively lower absorption into blood stream (Roncada et al., 2000), the therapeutic action is largely confined to uterine lumen and endometrium. Tetracycline's are known to be active under anaerobic conditions and are partly inactivated by purulent material, cell debris found in affected uterus (Cairoli et al., 1993).

However, currently in the United States, only ceftiofur hydrochloride, ceftiofur crystalline-free acid, and an injectable Oxytetracycline are labelled as treatment options for metritis. Systemic injection of PGF2α (PG) in cyclic cows causes Luteolysis of corpus luteum (CL) if present and this reduces the level of blood progesterone. Reduction in progesterone and increase of estrogen level cause estrus and result in myometrium contractions; these events are all plausibly favorable for clearance of uterine infection (Azawi 2008; LeBlanc 2008). The main advantages of this hormone are the time of injection, the ovarian structures, and the number of doses of PG that may improve reproductive performance in cows with endometritis (LeBlanc 2008). In cows with functional corpus luteum, administration of exogenous PGF2α is used to stimulate Luteolysis, which reduce the progesterone and increase the estrogen concentrations, induce estrus and resolve uterine infections (Murray et al., 1990; Lewis, 1997; Tenhagen and Heuwieser, 1999; Heuwieser et al., 2000; Laven, 2003). Exogenous PGF2α may enhance immune functions or increase uterine motility to help the uterus to resolve infections in animals that don't have active corpus luteum (Nakao et al., 1997; Hirsbrunner et al., 2003; Fernandes et al., 2014). However the results of therapy of endometritis with prostaglandins in the absence of an active corpus luteum are inconsistent (Steffan et al., 1984; Le Blanc et al., 2002b). It has been recorded that PGF2α has the least harmful effects and milk doesn't have to be discarded (Murray et al., 1990; Mansour et al., 2003). Successful treatment is evident by the clear vaginal discharge at subsequent estrus. Some reports indicate that PGF2α is more effective when progesterone levels are high or corpus luteum is palpable (Sheldon and Noakes, 1998; Le Blanc et al., 2002b). PGF2α was equal to (Sheldon and Noakes, 1998) or tended to be more effective (Steffan et al., 1984) than intrauterine penicillin or tetracycline for improvement of reproductive performance in cows with endometritis (Dubuc et al., 2011). Numerous reviewers have concluded that PGF2 appears to be at least as effective for endometritis as any available alternative therapy and presents minimal risk of harm to uterus or presence of residues in milk or meat (Paisley et al, 1986; Gilbert and Schwark, 1992; Olsen, 1996).

Note: Clinical cure rates were based on the absence of purulent discharge from the vagina and loss of other sign such as fever, dullness and other signs of toxemia**.**

MATERIALS AND METHODS

Study Area: The study was conducted at Livestock Research and Development Station Paharpur (located at 32°6'8N 70°58'12E and has an altitude of 173 meters (570 feet). D.I. Khan Khyber Pakhtun Khwa, Pakistan.

Animals: For this study total of 62 buffaloes (Naturally infected) having age of 4-8 years were selected from the same station. The buffalo's diet was composed of silage, wheat straw, Sadabahar, Barseem and concentrates (Shandar Wanda). These buffaloes did not receive any intrauterine or reproductive hormonal therapy for at least 14 days before clinical examination.

Clinical Examination

Buffaloes were examined 21–35 days in milk (DIM) and selected if they had a mucopurrulent vulvar discharge or uterus felt abnormal at rectal palpation**.** After inspection for the presence of fresh discharge around the vulva,

perineum, or tail, if discharge was not visible externally, vaginal examination was performed. After cleaning of the buffalo's vulva with a dry paper towel, a clean, lubricated, and gloved hand was inserted through the vulva. By palpation of all directions in the vagina, mucous contents of the vagina were withdrawn manually for examination. With respect to the color and proportion of pus in mucus, buffaloes were classified into two categories: (1) E1: clear mucus with flakes of pus, (2) clinical endometritis (E2andE3): clinical endometritis is characterized by the presence of purulent (>50% pus) or mucopurrulent (approximately 50% pus, 50% mucous) uterine exudate in the vagina, 21 days or more postpartum (Sheldon et al. 2006), mucopurrulent discharge or fluctuating contents in the uterus is grade 2 of endometritis (E2). Purulent discharge with or without palpable contents in the uterus is grade 3 of endometritis (E3) (Williams et al. 2005). Evaluation of vaginal discharge on the vulva, perineum, tail or in the vulva (by manual examination) was performed daily for each animal for seven weeks PP. The appearance of vaginal discharge was scored as follows: 0 = no discharge; 1 = clear mucus; 2 = mucus with the presence of pus; 3 = viscous purulent material; 4 = viscous haemopurulent discharge; 5 = watery mucohaemorrhagic malodorous secretion.

Treatment Protocols

At the first examination (28–35 DIM), Buffaloes with CE were randomly assigned to five groups (1) Oxytetracycline group (OTC): Buffaloes (n = 12) were allocated into this treatment group and received 5gm/ buffalo of 20% OTC (Retardoxi L.A) 25 ml intrauterine with disposable transcervical pipette (Ahmadi et al. 2005b). (2) Oxytetracycline+ Prostaglandin (OTC+ PGF2α) Buffaloes (n=12) with different endometritis grade were allocated in this group. Buffaloes in this group received 5gm/ buffalo of 20% OTC and If CL was present on ovaries after reproductive examination, 500 mcg of cloprostenol sodium (Cyclomate) was injected as IM route. (3) Ceftiofur Hydrochloride (CHR): Buffaloes (n=12) were allocated in this treatment group and received 600 mg (15 mL/d for 5 days) of ceftiofur Hydrochloride (Excefur 50mg/ml) intramuscularly (i. m). (4) Ceftiofur Hydrochloride+ Prostaglandin (CHR+ PGF2α) Buffaloes (n=15) with different endometritis grade were allocated in this group. Buffaloes in this group received 600 mg (15 mL/d for 5 days) of ceftiofur Hydrochloride (Excefur 50mg/ml) and If CL was present on ovaries after reproductive examination, two injection of 500 mcg of cloprostenol sodium (Cyclomate) was injected eight hours apart as IM route. (5)_Controlled_positive_Group; Buffaloes (n =11). Due to high spontaneous cure rates in CE (Noakes and England 2009), 11 untreated control buffaloes were allocated in to the control group .No placebo was used in this group. Estrus was detected three times daily by a technician and all the animals presenting signs of standing estrous were naturally mated with bull by artificial insemination (AI) technician. Pregnancy diagnosis was performed 60 days after natural service via rectal palpation and reconfirmation of pregnancy was made approximately 90 days after the Natural service. Fourteen days after treatment, all buffaloes were re-examined and sampling procedures were repeated. Results of treatment was considered by clinical treatment rate, defined as no vaginal discharge in reexamination after the first treatment and existence of corpus luteum on the ovary. Cytological cure rate was defined as the reduction in neutrophil numbers in the second examination. Reproductive performance was determined by measuring days to first service, days open, first service conception rate, conception rate to all services, Number of services per pregnancy and cows' pregnancy within 180 days in milk (DIM).

RESULTS

Clinical treatment rates in this examination (based on the absence of purulent discharge from the vagina in the second examination) were 75%, 83.33%, 67.33%, 73.33%, and 45.5% in OTC, OTC+PGF2a, CHR, CHR+PGF2a and control group, respectively. Clinical treatment rate was significantly lower in control group than in the OTC, OTC+PGF2a, CHR, CHR+PGF2a groups ($P \leq 0.05$). Clinical cure rate between five treatment groups can be compared by observing Tab.1. Clinical cure rate in the buffaloes with grade 1 endometritis was higher than in OTC, while E2 response was high to treatment in CHR and OTC+PGF2α groups, but this difference was not significant ($P \geq 0.05$). Number of days to first service was 88.66±20.49, 71.66±16.35, 98.5±16.46, 92.53±14.25 and 105±16.02 in OTC, OTC+PGF2a, CHR, CHR+ PGF2α and control groups respectively. Number of days opens was 118.83±15.01, 106.75±14.66, 135.08±19.58, 126.46±22.23 and 144.54±19.43 in OTC, OTC+PGF2a, CHR, CHR+PGF2a and control groups respectively. First service conception rate (%) and 2nd service conception rate (%) was 41.66% and 66.67 in OTC, 58.33% and 83.33% in OTC+PGF2a, 33.35% and 58.33% in CHR, 44.44% and 73 % in CHR+PGF2a and 27.27% and 54.54% in controlled group. Number of services per pregnancy 2.25±O.96, 1.8±0.74, 2.42±0.90, 2.09±0.89 and 2.7±0.69 in OTC, OTC+PGF2a, CHR, CHR+PGF2a and control groups respectively. Number of days to first services, days open and number of services per pregnancy was significantly lower in OTC+PGF2a group than control group while conception rate was high in OTC+PGF2a group than control group. In conclusion, the current study demonstrated improvement in post-partum reproductive performance in buffaloes treated with Oxytetracycline and prostaglandinF2α during the postpartum period.

Table 1
Clinical treatment rates (%) of grade 1 and clinical endometritis (E2 and E3) in five treatment groups in the second examination

Treatment Groups	Diagnosis 1	No of animals	Diagnosis 2 (%)	
	Endometritis Categories		Treated Endometritis	Buffaloes with Endometritis
OTC N=12	E1	5	4/5=80%	1/5=20%
	E2 & E3	7	5/7=71.42%	2/7=28.57%
	Total	12	9/12=75%	3/12=25%
OTC+PGF2α N=12	E1	3	2/3=66.66%	1/3=33.33%
	E2 & E3	9	8/9=88.88%	1/9=11.11%
	Total	12	10/12=83.33%	2/12=16.66%
CHR N=12	E1	5	3/5=60%	2/5=40%
	E2 & E3	7	5/7=71.4%	2/7=28.57%
	Total	12	8/12=67%	4/12=33%
CHR+PGF2α N=15	E1	8	6/8=75%	2/8=25%
	E2 & E3	7	5/7=71.4%	2/7=28.57%
	Total	15	11/15=73.33%	4/15=26.66%
CON N=11	E1	5	4/6=66.66%	2/6=33.33%
	E2 & E3	6	2/5=40	3/5=60%
	Total	11	6/11=54%	5/11=45.45

Table 2
Reproductive performance of animals treated with different antibiotic groups in case of clinical endometritis.

Treatment group (number of Animals)	Number of days to First Service	First Service Conception Rate (%)	2nd Service Conception Rate (%)	Number of Days Open	Number of services Per Pregnancy
OTC N=12	88.66±20.49	41.66	66.67	118.83±15.01	2.25±O.96
OTC+PGF2a N=12	71.66±16.35	58.33	83.33	106.75±14.66	1.8±0.74
CHR N=12	98.5±16.46	33.3	58.33	135.08±19.58	2.42±0.90
CHR+PGF2a N=15	92.53±14.25	44.44	73	126.46±22.23	2.09±0.89
CON N=11	105±16.02	27.27	54.54	144.54±19.43	2.7±0.69

DISCUSSION

A variety of antibiotics have been infused into the uterus to treat postpartum endometritis in dairy cows. OTC is one of the broad spectrum antibiotics that were used for treatment of postpartum endometritis in dairy cows (Ahmadi et al., 2005b; Sheldon et al., 2004). Moreover, because of its effective action in anaerobic environment of the uterus after parturition, OTC is one of the choices for intrauterine treatment of clinical endometritis (Kaczmarowski et al., 2003; Sheldon et al., 2004).Ahmadi et al (2005) reported that intrauterine infusion of OTC was better than 10 ml of Metri-Care (cephapirin) in treating early stages of postpartum endometritis (Ahmadi et al., 2005b). Although intrauterine OTC does not penetrate the wall of uterus well, it is not particularly effective against T. pyogenes and can have a direct irritant effect on the endometrium (Cohen et al., 1995).

In this study the Clinical treatment rates (based on the absence of purulent discharge from the vagina in the second examination) were 75%, 83.33%, in OTC and OTC+PGF2a group. This result was in agreement with AS Sultan (2005) who studied postpartum pyometra in Iraqi buffaloes. Number of days to first service was 88.66±20.49 and 71.66±16.35, in OTC, OTC+PGF2a group while Number of days opens was 118.83±15.01, 106.75±14.66, in OTC, OTC+PGF2a group. The conception rate was 66.67 and 83.33 % while Number of services per pregnancy2.25±O.96 and 1.8±0.74 in OTC, OTC+PGF2a group. A Sh Sultan (2005) who studied postpartum pyometra in Iraqi buffaloes stated that conception rate (86.6 %) and days open (82.7) by using PGF2α and Oxytetracycline 20% while Al-Hamedawi, T.M.; AL-Yasiri, E.S. and AL-Timimi, I.H. (2002). recorded days open 102 and services per conception 3.4 in postpartum bovine pyometra treated

with PGF2α and Oxytetracycline 20%. Malinowsk et al. (2004) reported that intrauterine therapy has been found effective in the prevention and prophylaxis of postpartum uterine diseases in cows. In the current research, the beneficial impact of PGF2α therapy on the shortened time from calving to uterine involution was shown to indicate these results in line with those reported by Tobolski et al. (2021). The present findings align with those reported by Kasimanickam et al. (2005), who observed that in dairy cows treated with a single PGF2α and antibiotics dose, the period from calving to conception was less than 101, 103 days compared to 119 days in control cows, respectively. Similar findings reported by Risco et al. (1994) showed that routine postpartum application of PGF2α decreases the time from calving to pregnancy in dairy cows. Goshen and Shpigel (2006) suggested that usage of intrauterine antibiotics in normal, treated, and untreated dairy cows with clinical metritis resulted in 140.5, 136.2, and 165.5 days of open days, respectively. Mcclary et al. (1989) treatment of dairy cows with PGF2α during early postpartum resulted in a decline in days open 98.6 days compared to 118.8, days for untreated cows. There were fewer days open for dairy cows treated with prostaglandin F2α (Folman et al., 1990). The dairy cows treated with PGF2α on day 8 postpartum recorded lower days open (White and Dobson 1990). Lopez-Gatius (2003) observed a drop in days open after administration of PGF2α during the early postpartum phase relative to the control group in dairy cattle. Cows with uterine disease (endometritis) recorded a longer interval (151 days) from calving to conception than unaffected dairy cows (119 days) (LeBlanc et al., 2002). Galvao et al. (2009) showed that PGF2α treatment in dairy cows with subclinical endometritis declines the time from parturition to conception. Bicalhoet al. (2016) reported that cows with subclinical endometritis had longer 42 days open compared to healthy cows. Kasimanickam et al. (2004) stated that in cows with subclinical endometritis the time from calving to pregnancy was longer 141 days compared to 112 days in healthy cows. Similar findings were reported by Gilbert et al. (2005) who found that in cows with subclinical endometritis the days open was longer 206 days compared to 118 days in healthy cows. Madoz et al. (2013) observed that cows with subclinical endometritis had an increase in the interval from parturition to conception compared with normal cows 133 and 93, days respectively. Galvao et al. (2009) reported that treatment with PGF2α in dairy cows with subclinical endometritis led to a decrease in the time from calving to pregnancy. Ricci et al. (2015) proposed that there was a 40-day delay to conception in beef cows with subclinical endometritis relative to normal cows. Vieira-Neto et al. (2014) proposed that cows with subclinical endometritis recorded a longer number of days open compared to healthy cows. Uterine disease results in an increase in the time from calving to pregnancy in multiparous cows (Toni et al., 2015). The time from calving to pregnancy (DO) extended in cows with postpartum uterine disorders such as subclinical endometritis (Barański et al., 2012). Barrio et al. (2015) found that the time from calving to conception (DO) was longer 154 days in cows suffering from subclinical endometritis compared with 119 days in healthy cows.

The clinical endometritis cure rate in this study was 67 and 73.33% in CHR, CHR+PGF2a groups respectively. Number of days to first service was 98.5±16.46 and 92.53±14.25 in CHR, CHR+PGF2a group while Number of days opens was135.08±19.58 and 126.46±22.23 in CHR, CHR+PGF2a group. The conception rate was 58.33 and 73% while Number of services per pregnancy was 2.42±0.90 and 2.09±0.89 in CHR, CHR+PGF2a group respectively. Julia Jeremejeva, Toomas Orro (2016) stated that total services conception rate in the early treated group was better than in the group treated in the late PP (93% and 71% in groups A and B2, respectively). The same tendency was seen in number of DO (100.7 ± 9.6 and 125.2 ± 14.1 in groups A and B2) and in NSP (1.4 ± 0.2 and 2.2 ± 0.4 in groups A and B2, respectively). But those differences were not significant, possibly because of not enough number of studied animals. The analysis of optimal sample size showed that this difference could be significant in case of more significant number of studied animals (at least 55 animals per group).

Clinical cure rate was 54% in controlled positive group which was in agreement with study of (Noakes and England 2009 who stated that there are high spontaneous cure rates in CE. The conception rate in control group was 54.54% while number of services per pregnancy was 2.7±0.69.

This positive effect of early administration of PGF2α has been found by numerous researchers (Nakao et al. 1997; Melendez et al. 2004; Jeremejeva et al. 2012). Nakao et al. (1997) treated endometritic animals with PGF2α on days 7 to 10 PP, and showed that the fertility parameters of treated cows were the same as in healthy control animals. Melendez et al. (2004) studied the effect of PGF2α on animals with acute puerperal metritis. They treated animals with an i.u. administration of ceftiofur with two doses of PGF2α, 8 h apart, on d 8 PP. Primiparous treated cows had smaller uterine diameters and lower uterine scores, reduced concentration of α1acid glycoprotein, and increased first service conception rate. In a previous study of Jeremejeva et al. (2012) the use of two injections of PGF2α, with an interval of 8 h, on the 8th day PP for treatment of acute puerperal metritis and endometritis had a positive effect on fertility parameters, which were as good as those in healthy animals. A single

subcutaneous administration of ceftiofur (1mg/kg) 24 h after calving resulted in peak concentrations of 2.85 ± 1.11 µg/mL at 2 h of administration and the concentration of ceftiofur in uterine tissues exceeded the minimal inhibitory concentration for common uterine pathogens (Okker et al., 2002). Consecutive administration of ceftiofur (1mg/kg IM) for 3 days to cows with clinical endometritis at 21-27 days in milk resulted in clear vaginal discharge at 41-42 days in milk (Kaufmann et al., 2010; Bartolome et al., 2014). A single IM administration of Oxytetracycline has been suggested to improve fertility in cows with subclinical endometritis (Tek et al., 2010).

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