

Comparison of *Pelargonium sidoides*, Placebo and Antibiotic Treatment of Chronic Endometritis in Dairy Cows: A Field Trial

¹S. Bademkiran, ²D. Kurt, ³B. Yokus and ⁴R. Celik

¹Department of Reproduction and Clinic for Obstetrics, ²Department of Physiology,

³Department of Biochemistry, ⁴Department of Animal Science,

Faculty of Veterinary Medicine, Dicle University, 21280, Diyarbakir, Turkey

Abstract: We compared the effects of the intrauterine application of an extract of *Pelargonium sidoides* (EPs 7630) to parenteral antibiotic injection in the treatment of chronic endometritis, which is commonly encountered postpartum in cows. Forty six cows diagnosed with chronic endometritis 21-27 days postpartum were selected and divided into three groups. Cows in group 1 (n = 16) received a physiological parenteral injection of 10 mL of serum per day for 3 days. Similarly, cows in group 2 (n = 15) received 1 mg kg⁻¹ ceftiofur (Ceftivil®) parenterally. Those in group 3 (n = 15) received an 8 mg (10 mL)/cow intrauterine dose of EPs 7630 (Umca®) for 3 days. When examined between the 35th and 41st day, clinical recovery rates were found to be as follows: for group 1, 1/16 (6.2%); for group 2, 8/15 (53.3%) and for group 3, 4/15 (26.69%). After this examination, cows whose chronic endometritis symptoms persisted according to clinical and rectal examination received a further 3 days of the treatment appropriate to their group. Later on various parameters were identified thus, for groups 1-3, respectively: insemination rate 87.5, 66.6 and 93.3%; days to first service 103.5, 91.0 and 96.0; first service conception rate 28.5, 40.0 and 35.7%; days open 140, 120 and 131 and cows pregnant within 250 DIM 56.25, 80.0 and 66.6%.

Key words: Cow, chronic endometritis, *Pelargonium sidoides*, herbal drug, ceftiofur, parenteral antibiotic

INTRODUCTION

Reproductive performance is a key component of dairy production management. Diagnosis and treatment of postpartum uterine disease and its putative impact on reproductive performance, have traditionally attracted considerable attention from veterinarians and producers (LeBlanc *et al.*, 2002a, b; Drillich, 2006). Under normal circumstances, many cows have some degree of postpartum uterine contamination. The natural resistance mechanisms of the uterus usually eliminate uterine infection and inflammation, but infection persists in 10-15% of the animals and causes subfertility even after resolution of clinical signs. A persistent postpartum uterine infection will result in poor reproductive performance (Kasimanickam *et al.*, 2005; Gilbert *et al.*, 2005; Kim *et al.*, 2005; Janowski *et al.*, 2001).

Chronic endometritis is also referred to as clinical endometritis and is characterised by the presence of mucopurulent or purulent exudate in the vagina 3 weeks or more after parturition. Chronic endometritis in cows is one of the most common postpartum disorders on

dairy farms. Depending on management and environmental conditions, i.e., deficiencies in hygiene at calving, dystocia, inadequate feeding of dry cows and infectious diseases, the average incidence of chronic endometritis is up to 37.5% (Drillich *et al.*, 2005, 2006; Foldi *et al.*, 2006; Kim *et al.*, 2005, Gilbert *et al.*, 2005).

Various studies have reported the isolation of various identifiable bacteria and Bovine herpes virus type four from the uterus in the first 10 after calving (Foldi *et al.*, 2006; Kasimanickam *et al.*, 2005; Drillich, 2006; Frazier *et al.*, 2001; Fabian *et al.*, 2008).

Much of the professional veterinary literature on bovine endometritis suffers from the lack of a universally accepted definition of the disease and associated uniformity in diagnostic criteria. The lactation incidence of endometritis has been variously estimated at 7.5-8.9%, based on visible mucopurulent vaginal discharge, 13.8% (unspecified diagnostic criteria), 7.8% (unspecified diagnostic criteria, including endometritis, metritis and pyometra 18% (rectal palpation), 3.4% (veterinary diagnosis), approximately 13% to over 40%. In addition,

the incidence of chronic endometritis also depends on the sensitivity of the diagnostic method and the time postpartum when the examination was performed (Drillich *et al.*, 2005; Gilbert *et al.*, 2005).

The treatment of chronic endometritis in dairy cattle has been under discussion for several years. The general principle of therapy for endometritis is to halt and reverse inflammatory changes that impair fertility. In practice, treatments aim to reduce the load of pathogenic bacteria and enhance the processes of uterine defense and repair. While, Knutti *et al.* (2000) and LeBlanc *et al.* (2002b) have stated that chronic endometritis has a tendency to recover without intervention with no negative impact on reproductive and performance, others have described a depressed fertility even for cases of subclinical endometritis (Gilbert, 1992; Kasimanickam *et al.*, 2004). Also, in recent publications, an intrauterine and parenteral treatment with antibiotics has been found effective (Drillich *et al.*, 2005, 2006; Drillich, 2006; Janowski *et al.*, 2001; Kasimanickam *et al.*, 2005; LeBlanc *et al.*, 2002b; McDougall, 2001; Foldi *et al.*, 2006).

Perhaps due to the limited success of antibiotics, substantial cost associated adverse effects and antibiotic resistance as a result of overuse and misuse, more attention is now focused on alternative treatments for various diseases. The use of alternative treatments is expanding in human medicine, but information about the extension of such practices to veterinary medicine is limited, as good records of the use of these treatments do not exist. In the treatment of farm animals, alternative therapies have been in focus mainly in relation to organic farming, because of the emphasis on natural methods and medicines to organic standards and the general objective of reducing the use of chemical substances (Agbabiaka *et al.*, 2008; Hektoen *et al.*, 2004).

Plant-derived antibacterials are always a source of novel therapeutics. A quick look at the way nature, especially plants, tackles the problem of infection will provide a deeper understanding of the methodology, which needs to be adopted for the design and development of novel highly effective anti-infectious agents in general and antimycobacterials in particular. The scarcity of infective diseases in wild plants is in itself an indication of the successful defense mechanisms developed by them (Hemaiswarya *et al.*, 2008).

Extract of *Pelargonium sidoides* (EPs 7630) is still the subject of considerable research aimed at establishing the chemical and pharmacological basis of its therapeutic activity, which has been demonstrated in a number of clinical studies. A detailed investigation of the root extractives of *P. sidoides* has been initiated in order to

provide a chemical rationale for its popularity in traditional medicine and its present utilisation in phytomedicine. It has been reported in recent studies that this extract is dominated by the presence of highly oxygenated coumarins, simple phenols with gallic acid as the principal plant metabolite and high molecular weight proanthocyanidins. Pharmacological studies have demonstrated antibacterial and immunomodulatory activities for these chemical constituents *in vitro* (Kolodziej *et al.*, 2003; Wittschier *et al.*, 2007).

The alcoholic extract of the root of *Pelargonium sidoides* has been shown to have some anti-bacterial and antiviral effects (Bereznoy *et al.*, 2003; Kolodziej and Kiderlen, 2007; Wittschier *et al.*, 2007).

Based on present knowledge, interest has focused on a moderate antimicrobial activity and immunomodulatory effects via increased NK-cell formation and TNF- α -, iNO- and INF- β release as the main therapeutic principles. It can be seen from the antimicrobial effects that the minimal inhibitory concentrations for the potentially active compounds are in a range higher than 0.2 mg mL⁻¹ and also the extracts exhibit MICs in a range from 0.6-10 mg mL⁻¹ (Wittschier *et al.*, 2007).

The objective of this study was to evaluate the intrauterine use of EPs 7630 for the treatment of chronic bovine endometritis in a field trial in comparison with a systemic administration of antibiotic (ceftiofur). The treatment of chronic endometritis with herbal extracts of *Pelargonium sidoides* has never before been evaluated in a controlled field study in cattle reproduction. The criteria for the efficacy of the treatment protocols were clinical cure rate, defined as no vaginal discharge at the re-examination.

MATERIALS AND METHODS

The study was conducted on a commercial dairy herd in Diyarbakir, Turkey. Six red home breed South Anatolian cows and 40 Holstein hybrids were used for the study. All the cows in the study were kept tied in a barn. They were nourished with wheat straw-bran and wheat-straw-barley. No different nourishment program was applied according to the physiological condition of the cows. Seven days after calving, cows were grouped in freestall facilities. The examination protocol and other details of the study have been reported previously by LeBlanc *et al.* (2002a, b), Dirillich *et al.* (2005), Drillich (2006), Amiridis *et al.* (2003) and Janowski *et al.* (2001). All cows were examined by external inspection and palpation of the genital tract per rectum

between 21 and 27 days in milk (DIM; exam 1). History of veterinary assisted parturition, twin birth, retained placenta for >24 h, or metritis (systemic illness referable to uterine infection) in the current lactation were recorded. The size of the uterine horns, fluctuating contents and vulval discharge was recorded. Vaginal discharge and/or fluctuating contents in the uterus were regarded as clinical signs for chronic endometritis. Endometritis was classified in three categories: clear mucus with flakes of pus (E1), mucopurulent discharge or fluctuating contents in the uterus (E2) and purulent discharge with or without palpable contents in the uterus (E3) (Table 1).

Cows with signs of endometritis were enrolled into one of the three treatment groups according to the last digit of the ear-tag number of the cows. Upon diagnosis, animals in group 1 immediately received a placebo intramuscularly (i.m.) (10 mL serum) on three consecutive days and in group 2 cows with endometritis received a systemic antibiotic treatment with 1 mg kg⁻¹ of ceftiofur (Ceftivil[®], Vilsan, Turkey) intramuscularly (i.m.) on 3 consecutive days.

Cows in group 3 received an intrauterine treatment with 8 mg (10 mL) of EPs 7630, Umca[®] (Dr. Willmar Schwabe GmbH and Co. ISO Pharmaceuticals, Ettlingen, Germany). The product was applied in 190 mL of serum fizyologic by a disposable catheter as used for intrauterine catheter on three consecutive days. Products were stored and handled according to label directions. All cows with endometritis were re-examined 14 days later (35-41 DIM)

by palpation of the genital tract per rectum (Exam 2). Cows with symptoms of endometritis were re-treated according to their groups at Exam 2 (Table 2).

The voluntary waiting period was set at 72 DIM. All cows were examined 68-74 DIM by palpation of the genital tract per rectum. Cows were naturally inseminated on observed estrus. Pregnancy Diagnosis (PD) was performed 38-44 days after natural insemination. Cows not inseminated by 100 DIM and cows inseminated but not pregnant at PD were examined by palpation of the genital tract per rectum (fertility exam). The fertility exam was repeated at 14 days intervals until the cows were inseminated. The outcome of the treatment was assessed by clinical cure rate, defined as no vaginal discharge at the re-examination after the first treatment and by reproductive performance measures in the current lactation. Reproductive performance measures and their definitions are described in Table 3.

Statistical analysis was performed using the SPSS package. Cows inseminated, first service conception rate and conception rate to all services (Cows pregnant within 250) were compared using Chi-square (χ^2) analysis. Days to first service and days open were compared using the Duncan test.

Table 1: Classification of endometritis at 21-27 DIM (Exam 1) in groups control, Ceftiofur and EPs 7630

Classification	Control (n:16)	Ceftiofur (n:15)	EPs 7630 (n:15)
Endometritis (E1%)	9 (56.2)	8 (53.3)	7 (46.6)
Endometritis (E2%)	5 (31.2)	4 (26.6)	5 (33.3)
Endometritis (E3%)	2 (12.5)	3 (20.0)	3 (20.0)

Table 2: Diagnoses at 35-41 DIM (exam 2) for 3 categories of endometritis at 21-27 DIM (exam 1) in groups control, ceftiofur and EPs 7630, respectively

Groups	Diagnosis exam 1	Diagnosis exam 2							
		No. endometritis		Endometritis (E1)		Endometritis (E2)		Endometritis (E3)	
		n	(%)	n	(%)	n	(%)	n	(%)
Control	E1 n: 9	1	11.1	8	12.5	0	00.0	0	00.0
	E2 n: 5	0	00.0	2	40.0	3	60.0	0	00.0
	E3 n: 2	0	00.0	0	00.0	1	50.0	1	50.0
Total	n:16	1	6.2	10	62.5	4	25.0	1	6.2
Ceftiofur	E1 n: 8	6	75.0	2	25.0	0	00.0	0	00.0
	E2 n: 4	2	50.0	1	25.0	1	25.0	0	00.0
	E3 n: 3	0	00.0	1	33.3	2	66.6	0	00.0
Total	n:15	8	53.3	4	26.6	3	20.0	0	00.0
EPs 7630	E1 n: 7	3	42.8	4	57.1	0	00.0	0	00.0
	E2 n: 5	1	20.0	2	40.0	2	40.0	0	00.0
	E3 n: 3	0	00.0	1	33.3	1	33.3	1	33.3
Total	n:15	4	26.6	7	46.6	3	20.0	1	6.6

Table 3: Reproductive performance measures for groups control, ceftiofur and EPs 7630, respectively

Parameters groups	Cows inseminated (%)	Days to first service (means±SE)	First service conception rate (%)	Days open (means±SE)	Cows pregnant within 250 DIM (%)
Control	87.5		28.5		6.25
Total (n:16)	(14/16) ^a	103.5±2.01 ^a	(4/14) ^a	140±7.97 ^a	(9/16) ^a
Ceftiofur	100.0		40.0		80.0
Total (n:15)	(15/15) ^a	91.0±1.26 ^b	(6/15) ^a	120±7.43 ^a	(12/15) ^a
EPs 7630	93.3		35.7		66.6
Total (n:15)	(14/15) ^a	96.0±1.06 ^c	(5/14) ^a	131±8.01 ^a	(10/15) ^a

Values in rows with different letters (a-c) differ significantly (p<0.01)

RESULTS AND DISCUSSION

This study was designed to compare the administration of extract of *Pelargonium sidoides* (EPs 7630) and ceftiofur hydrochloride on chronic endometritis.

The prevalence of chronic endometritis during the study period was within the range observed in other studies that based the diagnosis of endometritis on palpation of the genital tract per rectum (Drillich *et al.*, 2005; Gilbert *et al.*, 2005; Foldi *et al.*, 2006). LeBlanc *et al.* (2002a) and Gilbert *et al.* (2005) have emphasized that diagnoses by a combination of external inspection, vaginoscopic examination and palpation of the cervical diameter have a higher predictive value regarding time to next pregnancy than palpation of the uterus alone. With a more precise diagnostic method, i.e., vaginoscopic examination, cytology or ultrasound, more cows with signs of mild endometritis would probably have been found. We adopted the diagnosis of chronic endometritis based on the criteria laid out by these researchers.

It has been often discussed that chronic endometritis in dairy cattle has a tendency to be cured without intervention (LeBlanc *et al.*, 2002a; Drillich *et al.*, 2005; Knutti *et al.*, 2000). However, it was found that the difference between groups in various measurements made in this study was statistically insignificant. In spite of this, when the treatment groups were compared it was seen that there were unfavourable results for cows in the control group such as low scores for length of time period for days to first service, days open, cows pregnant within 250 DIM and first service conception rate. For this reason, we think that contrary to what is claimed, chronic endometritis in cows does have an adverse effect on reproductive parameters.

Fabian *et al.* (2008) identified BoHV-4 in 87.1% of cows with endometritis, but they were unable to obtain definite evidence of its role in the etiology of this disease. Nevertheless, research into the effectiveness of drugs with an antiviral and immunomodulatory effect such as extract of the root of *Pelargonium sidoides* (EPs 7630) in cases of endometritis could give interesting results.

Currently, many different treatments are applied to endometritis in dairy cows (Janowski *et al.*, 2001; Amiridis *et al.*, 2003). Local versus systemic administration of antibiotics has been the subject of a long debate. An intrauterine treatment leads to high concentrations of the drug in the uterine cavity and the endometrium and a relatively small amount is absorbed into the systemic circulation. Systemic administration of antibiotics results in concentrations in the uterine tissue

and lumen that are at best comparable to plasma levels and which often do not reach minimal inhibitory concentrations against uterine pathogens. Other disadvantages of parenteral treatment are the higher total quantities of antibiotics needed to reach similar concentrations. More generally, a systemic antimicrobial treatment is not justified as long as the infection remains localised to the uterus (Foldi *et al.*, 2006). According to the results of these studies, it can be seen that parenteral treatment can be as effective as intrauterine treatment in cases of chronic endometritis, given the choice of a suitable antibiotic.

LeBlanc *et al.* (2002b) state that between 27 and 33 DIM, cows with endometritis treated with cephalosporins i.u. had a significantly shorter time to pregnancy than untreated cows. The results of this study suggest that the values obtained by these writers are correct, because it can be seen in this study that the cows with chronic endometritis in the treatment groups conceived in a shorter time and the number of pregnant cows in these groups was lower than in the control group.

In the last few years, there has been a trend towards the increased use of alternative medicine in animals. Treatment of this type has several advantages: the low cost of the treatment, efficacy against a variety of disorders and the absence of side effects. In farm animals (cattle, pigs, poultry, etc.), the improvement of production potential and the absence of residues following such treatment constitute two further major advantages. Intrauterine treatments with antibiotics and disinfectants, e.g. Lugol's iodine, are still widespread in Europe, although, several studies have shown no benefits on reproductive performance from this treatment. An ideal treatment of endometritis should eliminate bacteria in the uterine cavity and in the subendometrial layers, should not inhibit the normal uterine defense mechanisms and have no withdrawal period for milk. However, the use of antibiotics and hormones in food-producing animals is increasingly under critical discussion in the public and political arena (Drillich *et al.*, 2005; Drillich, 2006; Janowski *et al.*, 2001; Foldi *et al.*, 2006).

Despite the fact that many researchers have stated the disadvantages of the use of antibiotics in the treatment of endometritis, this study obtained the best results with the use of parenteral antibiotics. However, we feel that research is needed into the use of alternative treatment methods to minimize the economic losses arising because milk produced when antibiotics are being used is unsuitable for human consumption.

Conrad *et al.* (2007) state that in investigations EPs 7630 *in vitro* has shown positive effects on the activity of human peripheral blood phagocytes. There are three

important parameters that characterize phagocyte activity: ingestion of the pathogen (phagocytosis), release of reactive oxygen species (oxidative burst) in order to aggrieve the ingested microorganism and eventual elimination of the pathogen (intracellular killing). However, we feel that our results are insufficient for us to offer a definite opinion and that the drug must be used in parenteral and *in vivo* conditions in order to establish any such effect.

Because of the limitations of the diagnostic methods used in veterinary practice, cure rate is based only on clinical symptoms. Therefore, the efficacy of a treatment for endometritis in dairy cows must also be evaluated by reproductive performance. In order to assess, the outcome of the treatment protocols, reproductive performance measures for two treatment groups and a healthy control group were compared (Drillich *et al.*, 2005). It could be seen in this study that clinical cure provided important information on the effectiveness of treatment.

In a scan of the literature, no reference to the use of herbal medicine to treat bovine endometritis was found. However, Hektoen *et al.* (2004) found in a study of mastitis that there was no difference in recovery rates between cases where, herbal treatment was used and the use of antibiotics. Nevertheless, when the results of this study are examined, it may be logical to consider the choice of EPs 7630 as an alternative treatment if antibiotics are not to be used because of their possible side effects.

CONCLUSION

In veterinary practice, the treatment of chronic endometritis is usually based on prostaglandin $F_2\alpha$ and its analogues, an intrauterine infusion of broad-spectrum antiseptics or antibiotics. However, the use of hormones and antibiotic drugs in food-producing animals is under critical public discussion. This requires research for new therapeutic strategies. The present study is the first to evaluate the treatment of chronic endometritis with a herbal drug extract of *Pelargonium sidoides*. However, in this study there was no evidence that herbal extracts of *Pelargonium sidoides* played a useful curative role in chronic bovine endometritis.

From the results of this study, it can be concluded that antibiotics are still the treatment of choice for chronic endometritis in dairy cows.

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