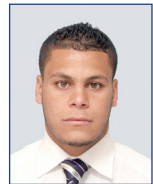


Cefacetrile and Rifaximin association might improve first service conception rate and reduce the number of services per conception in cows with clinical endometritis



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Abstract

Clinical endometritis (CE) is a serious disease leading to poor reproductive performances in lactating dairy cows, thus diminishing farm profitability. To preserve optimum reproductive efficiency, various strategies and therapeutic approaches have been proposed to manage cows with CE, often with contradictory results. Thus, investigating new paths to CE treatment is economically important. The aim of the present study was to test the efficacy of three therapeutic protocols on the clinical cure rate of CE, and improvement of reproductive performance. Cows with CE ($n=42$), 21–38 days in milk (DIM), were assigned to three treatment groups: **PGF**: cows ($n=19$) were treated systemically with two doses of d-cloprostenol, a $\text{PGF}_{2\alpha}$ analogue, at 14-days intervals; **CEFAX**: cows ($n=10$) received an intrauterine infusion of the combined antibiotics Cefacetrile and

Rifaximin; and **NAX**: cows ($n=13$) received systemic treatment with Ceftiofur crystalline free acid (CCFA). A control group included cows ($n=36$) free from CE (healthy group: **HE**). All cows were clinically re-examined after the end of the treatment protocol. The clinical cure rate was 73.7%, 80% and 69.2% in PGF, CEFAX, and NAX groups, respectively ($P>0.05$). The HE group had a significantly shorter calving to first service interval compared to CEFAX and PGF groups ($P<0.05$), however the difference was not significant with NAX group. The mean calving to fertilizing service interval (CFI) was slightly higher in all three treatment groups compared to the HE group, however the difference was not significant ($P>0.05$). CEFAX protocol resulted in shorter but not statistically significant CFI, compared to the PGF and NAX protocols. Services per conception rate were slightly lower (1.7) in the

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CEFAX group compared to HE (1.75), PGF (1.84) and NAX (2.23) groups, however these differences were not significant. First service conception rate and conception rate at 105 DIM did not differ statistically between the treatment groups. While the difference was not significant, CEFAX protocol had slightly

better cure rate for CE, reducing the number of services per conception and boosting the resumption of ovarian activity after calving. Validating these findings on a larger herd size will improve the accuracy of these findings.

Key words: *clinical endometritis; treatment; cure rate; reproductive performance*

Introduction

During parturition and soon after calving, in most cows, the uterus is invaded mainly by commensal and opportunistic bacteria (*i.e. Escherichia coli, Trueperella pyogenes, and Fusobacterium necrophorum*) (Williams et al., 2005; Malinowski et al., 2011; Brick et al., 2012; Szenci et al., 2018). Uterine involution is the physiological process leading to epithelium regeneration, endometrial repair, microbial clearance of the uterine lumen and resumption of ovarian activity (Sheldon, 2004; Kočila et al., 2013; Sheldon and Owens, 2017).

Several clinical trials have shown that clinical endometritis (CE) declines reproductive efficiency in dairy cows, indirectly lowering farm profitability (Kim and Kang, 2003; Brick et al., 2012; Giuliadori et al., 2013; Đuričić et al., 2014). CE is an afebrile inflammation of the endometrium, diagnosed by the detection of abnormal uterine discharges in the vagina beyond 21 days in milk (DIM) (Sheldon et al., 2006). The disease is highly prevalent, affecting about 40% of lactating dairy cows (Kaufmann et al., 2010; Ahmadi et al., 2019).

The diagnosis of CE can be conducted by rectal palpation searching for uterine fluctuation or by vaginal examination (e.g. vaginoscopy or Metrichick®) based on clinical symptoms, mainly pus and a fetid odour of vaginal discharges (VDs) (Runciman et al., 2009). Furthermore, CE can be diagnosed subclinically by uterine biopsy or cytology to detect uterine

inflammation (Földi et al., 2006). Once CE is diagnosed, a good treatment protocol should be applied. However, CE therapy is greatly debated in the context of its effect on reproductive performances of dairy cows (*i.e.*, first service conception rate (FSCR), calving to first service interval (CFSI), calving to fertilizing service interval (CFI), and number of services per conception (NSPC)). Treatment effectiveness depends on the medicines administered, postpartum period of treatment, stage of uterine involution, and ovarian activity (Lefebvre and Stock, 2012). Various remedies have been proposed, including uterine antibiotics (Mari et al., 2012; Tison et al., 2017), systemic antibiotics (Kaufmann et al., 2010; Brick et al., 2012), antiseptics (Mido et al., 2016), enzymes (Drillich et al., 2005), dextrose (Brick et al., 2012; Ahmadi et al., 2019), liquid paraffin (Makki et al., 2017), nonsteroidal anti-inflammatory drugs (NSAIDs) (Königsson et al., 2001), hormones (e.g. PGF_{2α}) (Kasimanickam et al., 2005) and homeopathic remedies (Arlt et al., 2009), all of which have been widely tested.

The aim of the present study was to compare the clinical cure rate of three therapeutic protocols using systemic prostaglandin (PGF_{2α}) analogues (d-cloprostenol), intrauterine application of intramammary applicators composed of an antibiotic association (Cefacetrile+Rifaximin), and a systemic antibiotic (Ceftiofur crystalline free acid:

CCFA) in cows suffering from CE, and to assess the effects of these protocols on reproductive performance in comparison with healthy cows.

Materials and methods

Animals

The study was conducted between April 2018 and December 2019 on six dairy farms in Sougueur, in central-west Algeria. All farms had an annual breeding system, and no synchronization programmes for oestrus or ovulation were used. Cows were housed in loose housing system with a similar feeding system (the ration consisted of meadow fodder or corn silage with vetch oats hay, and commercial concentrates were added according to milk yield). Water was given *ad libitum*. Animals were milked twice a day and the average daily milk production was 13.7 ± 0.6 kg/cow. The body condition score (BCS) of the selected animals ranged between 2.75 and 3.25 according to criteria proposed by Ferguson et al. (1994).

Gynaecological examination and enrolment criteria

Only cows between 21 and 38 DIM (Exam 1) were included in the study. The perineal region was clinically inspected to detect abnormal VD_s, while rectal palpation and vaginoscopy were used to determine the origin of VD_s (Plöntzke et al., 2011). Transrectal ultrasound examinations (Dramanski I-Scan, Dramanski® animal profi, Poland) were performed to monitor uterine liquid accumulation, wall thickness, uterine lumen diameter and ovarian structures. VD_s were scored according to Williams et al. (2005). Cows with VD_s ≥ 1 were considered as having CE (Madoz et al., 2017; Tison et al., 2017). Cows having vaginal laceration at calving or were subject to caesarean section and/or received any intrauterine or systemic

antibiotic or hormonal treatment during the last 15 days before the start of the study were excluded. After the onset of the experimental study, any cow receiving a treatment for other diseases than CE was excluded. Cows that were culled or sold before the pregnancy diagnosis were excluded from the analysis.

Treatment protocols

Cows were randomly allocated to four experimental groups, as follows. The PGF protocol included 19 cows that received two intramuscular injection of 150 µg d-cloprostenol a PGF_{2α} analogue (Dalmazin®, FATRO S.p.A. Veterinary Pharmaceutical Industry, Via Emilia, 285, 40064 Ozzanodell'Emilia (Bologna), Italy) at 14-day intervals. The CEFAX protocol included 10 cows that received simultaneous intrauterine infusion of two intramammary applicators (Cefaximin-L spray®, FATRO S.p.A., Italy). Each 15 g applicator contains the antibiotic association of Cefacetrile (200 mg) and Rifaximin (100 mg), the mixture was infused in the uterus using a solid stainless-steel rod of 50 cm in length. The NAX protocol included 13 cows that received a single dose of 6.6 mg/kg of bodyweight (BW) of CCFA subcutaneously behind the ear (Naxcel®, Zoetis, USA). The HE group included 36 healthy cows without clinical symptoms of CE. To determine the cure rate of protocols, all treated cows were re-examined two weeks after the end of the treatment (Exam 2) (35–53 DIM). The clinical cure was defined as a cow with CE at Exam 1 that was subsequently described as clinically healthy (VD_s=0) at Exam 2. Reproductive parameters were defined and are summarized in Table 1. The voluntary waiting period was set at 50 days postpartum, and pregnancy controls were performed by transrectal ultrasonography at 35±4 days post mating. The study was carried

Table 1. Definitions of reproductive parameters for evaluating the effect of the treatment protocol in dairy cows

| Parameters | Definition |
|--|---|
| Cure rate (%) | The number of cured cows on day 14 divided by the number of treated cows in each group*100 |
| Calving to first service interval (CFSI) (days) | The number of days from calving to first service |
| Calving to fertilizing service interval (CFI) (days) | The number of days from calving to successful service |
| Number of services per conception (NSPC) | The number of services required to get a cow pregnant |
| First service conception rate (FSCR) (%) | The number of cows get pregnant at first service divided by the total number of serviced cows*100 |
| Conception rate at 105 DIM (CR105) (%) | The number of pregnant cows until 105 days divided by the total number of mated cows *100 |

out according to the guidelines of the Institutional Animal Care Committee of the Algerian Higher Education and Scientific Research.

Statistical analysis

Data were analysed using IBM SPSS version 24.0. (IBM SPSS Statistics for Windows, Version 24, USA). Cure rate, first service conception rate (FSCR), and conception rate until 105 DIM (CR105) were compared among the experimental groups using the Chi-square test or Fisher's exact test. Reproductive parameter data (calving to first service

interval (CFSI), calving to fertilizing service interval (CFI), and number of services per conception (NSPC)) were presented as means \pm standard deviation (SD), and the Mann-Whitney nonparametric U-test was used for statistical comparison between groups. Statistical significance was set at $P < 0.05$.

Results

The clinical cure rate of CE cows was 73.7%, 80% and 69.2% for PGF, CEFAX, and NAX protocols, respectively ($P > 0.05$). FSCR did not differ significant between

Table 2. Cure rate and reproductive performances indices in the control and treatment protocols.

| Parameters | Healthy | PGF | CEFAX | NAX |
|---------------------------|--------------------------------|--------------------------------|-------------------------------|------------------|
| Cure rate % (n) | - | 73.7 (14/19) | 80 (8/10) | 69.2 (9/13) |
| FSCR% (n) | 36.1 (13/36) | 36.8 (7/19) | 40 (4/10) | 23.1 (3/13) |
| CR105 (n) | 86.1 (31/36) | 73.7 (14/19) | 70 (7/10) | 69.2 (9/13) |
| CFSI (mean \pm SD) days | 59.94 \pm 11.64 ^a | 75.21 \pm 27.08 ^b | 69.90 \pm 8.42 ^b | 67.69 \pm 13.2 |
| CFI (mean \pm SD) days | 76.50 \pm 17.74 | 93.32 \pm 35.43 | 85.70 \pm 21.25 | 94.0 \pm 30.92 |
| NSP (mean \pm SD) days | 1.75 \pm 0.69 | 1.84 \pm 0.83 | 1.70 \pm 0.67 | 2.23 \pm 1.01 |

Values in lines with different letters (^{a,b}) are significantly different ($P < 0.05$). FSCR = First service conception rate; CR105= Conception rate at 105 DIM; CFSI = calving to first service interval; CFI= calving to fertilizing service interval; NSPC= number of services per conception

any treatment protocol and the control group ($P>0.05$). The lowest FSCR was found in the NAX group (23.1%). The highest CR105 was found in the HE group (86.1%), however the difference was not significant between any treatment protocols and the control group ($P>0.05$). CFSI was significantly higher in both the PGF (75.21±27.08) and CEFAX groups (69.90±8.42) compared to HE group (59.94±11.64) ($P<0.05$). Compared to the HE group, CFI was about 17 days (d), 9d, and 18d longer in the PGF, CEFAX and NAX groups, respectively, though differences were not significant ($P>0.05$). NSPC was slightly lower (1.7) in the CEFAX group compared to the HE (1.75), PGF (1.84) and NAX (2.23) groups, though differences were not significant ($P>0.05$) (Table 2).

Discussion

Clinical endometritis is an important postpartum uterine disease that alters normal reproductive performance, reducing subsequent fertility and thus has a negative impact on the farm profitability. The aim of this study was to evaluate the effect of different treatment protocols in cows with CE on the clinical cure rate and reproductive performance.

The selected protocols were based on *in vitro* findings where Ceftiofur, a third generation cephalosporin, Cephapirin, a first generation cephalosporin, and Rifaximin, a semi-synthetic antibiotic, were concluded to be effective in the treatment of uterine infection (Malinowski et al., 2011). The three molecules are broad spectrum antibiotics and active against gram-positive and gram-negative bacteria, even in an anaerobic environment. Furthermore, Galvão et al. (2009), reported that using intramammary applicators of Ceftiofur (125 mg) by intrauterine route resulted in concentrations of Ceftiofur in uterine fluids ($>0.50 \mu\text{g/mL}$) sufficient to inhibit growth of relevant pathogens involved in uterine infections during

the first two months of calving (Witte et al., 2011). Since CE is a pathological inflammation of the endometrium, Flammini et al. (2018) revealed surprising anti-inflammatory properties of Rifaximin on the bovine endometrial cell challenged with Lipopolysaccharide (LPS) of *Escherichia coli*.

The prostaglandin $F_{2\alpha}$ has been commonly used as remedy for postpartum diseases. Several studies have revealed that $PGF_{2\alpha}$ and its analogues effectively improve reproductive performance and increase the cure rate of uterine diseases (Ahmadi et al., 2018), especially those associated with the presence of *corpus luteum* (CL). In the literature, it seems that using two injections of $PGF_{2\alpha}$ at a 14-day interval is the most common and effective therapeutic protocol for CE (Lefebvre and Stock, 2012). The use of $PGF_{2\alpha}$ in CE therapy is intended to induce luteolysis of CL, boost uterine contraction and thus accelerate the uterine involution and the resumption of ovarian activity, which will reduce the occurrence of CE (Hoedemaker, 1998; Kasimanickam et al., 2005). Furthermore, $PGF_{2\alpha}$ has immunological properties, as it increases uterine leukotriene B4 secretions that supports chemotaxis, cell-mediated cytotoxicity, phagocytosis, and lymphocyte function, all of which will control and modulate uterine inflammation (Slama et al., 1993; Lefebvre and Stock, 2012). Although, it has been demonstrated that a systemic antimicrobial treatment of CE is not justified since the possible infection in the case of CE is limited to the superficial layer of the endometrium (Földi et al., 2006), Kaufmann et al. (2010) reported that systemic treatment with 1.0 mg/kg BW of Ceftiofur over three consecutive days in cows with signs of clinical endometritis 21–27 DIM had the same effect as treatment with two doses of $PGF_{2\alpha}$ at a 14-day interval. Also, systemic antibiotic administration may provide equal distribution of a therapeutic concentration to different

organs, preventing possible passage of bacteria to the uterus. Witte et al. (2011) reported that subcutaneous administration of CCFA (6.6 mg/kg BW) after parturition for healthy puerperal dairy cows with normal parturition resulted in effective and durable concentrations of Ceftiofur derivatives in endometrial tissues and lochia that exceed the recommended minimal inhibitory concentrations for many pathogens detected in genital tract pathologies, mainly *Escherichia coli*, *Trueperella pyogenes*, *Fusobacterium necrophorum* and *Prevotella melaninogenica*. In their study, the mean concentration of desfuroylceftiofur acetamide, the active metabolite of Ceftiofur reached its highest level in the endometrial tissue 24 h after systemic administration of CCFA, and remained high until day 7, after which it started to decline.

In the current study, the clinical cure rate in the three treatment groups was around 70%. These results indicated that the three treatments helped to clinically resolve CE. In a previous study, the clinical cure rate of systemic Ceftiofur or two doses of PGF_{2α} was 74.2% and 80.2%, respectively (Kaufmann et al., 2010), which is similar to our findings. Also, Mari et al. (2012) established a scoring system for evaluating CE severity where a higher score indicates a more severe case of CE. The authors found that intrauterine infusion of 500 mg Cephapirin, a first generation cephalosporin having similar activity to Cefacetrile, decreased the score value from 5.91 to 1.0 three weeks after treatment. The likelihood for clinical cure decreased with VD score (Eslami et al., 2015) and the severity of endometrial lesions and the detection of *Trueperella pyogenes* (Madoz et al., 2017).

The conception rate of the HE group and treated cows did not differ significantly among groups at 105 DIM (71.4% in average for treated groups vs 86.1% in HE group) ($P>0.05$). This result is consistent with Ahmadi et al.

(2018), who found that the percentage of pregnant cows at 100 and 200 DIM was similar among groups (46% in average at 100 DIM and 82% at 200 DIM). Soon after calving, cows are inevitably exposed to a negative energy balance that affects the effectiveness of immune function and metabolism, resulting in several diseases (Giuliodori et al., 2013). However, adjusting animal feeding is effective in reducing the effects of negative energy balance and preventing BCS loss (Galvão, 2013).

To be highly effective, CE treatment should not only increase the cure rate but also improve the reproductive performance of the female. Cows in the HE group had a significantly shorter CFSI compared to the three treatment groups. The median time to first service was about 15d, 10d, and 8d higher in the PGF, CEFAX and NAX groups, respectively. CE is an inflammation of the endometrium and often associated with disruption of the endometrial epithelium and reduction and dysfunction of endometrial glands (Sheldon et al., 2009b; Adnane et al., 2018), extending uterine involution and delays the resumption of normal ovarian activity and pregnancy (Tison et al., 2017).

While the difference was not significant, the highest number of services per conception was shown in NAX groups compared to the other groups. This could be explained by the fact that the effective concentration of the antibiotic did not reach the endometrium in the appropriate time and for the required duration, or the endometrium was affected by pathogens resistant to Ceftiofur (Malinowski et al., 2011). Santos et al. (2010) reported that 38.9% of *Trueperella pyogenes* isolates were resistant to Ceftiofur. Likewise, intrauterine infusion of Ceftiofur reduced bacterial contamination of the uterus, decreased the prevalence of CE but failed to reduce the prevalence of subclinical endometritis

(Galvão et al., 2009). Since endometritis is a pathological inflammation and the causative relation with bacteria is highly debated, many researchers assumed that even after the resolution of clinical symptoms of the disease, subfertility associated with endometritis persists (Eslami et al., 2015), and subclinical endometritis may develop (Sheldon et al., 2009a). Unfortunately, we did not diagnose subclinical endometritis as it was beyond the scope of this study. The cytological cure rate based on the neutrophil level in the endometrium was higher in cows with CE that received intrauterine Cephapirin or systemic PGF_{2α} at 28–35 DIM compared to untreated cows (Makki et al., 2017). Therefore, associating the cytological cure rate with the clinical diagnosis would assist in determining which treatment protocol is more effective for CE treatment.

Conclusion

According to its effect on cure rate and reproductive performances, treatment with Cefaximin-L spray® intramammary applicators helped to resolve CE in dairy cows and to slightly improve the reproductive performances. We could not investigate the cytological cure rate as subclinical endometritis was not diagnosed. Further research on a larger sample size is planned to overcome this limit, as we believe that the reproductive parameters remained lower than normal due to the presence of subclinical inflammation in those animals, which required treatment other than antibiotics. Modulating uterine inflammation would be the next step toward endometritis management.

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Kombinacija cefacetrila i rifaksimina može poboljšati postotak prvog uspješnog osjemenjivanja i smanjiti broj osjemenjivanja po koncepciji u krava s kliničkim endometritisom

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Klinički endometritis (CE) jedna je od glavnih značajnih bolesti koja dovodi do lošeg reproduktivnog učinka mliječnih krava u laktaciji, a time smanjujući profitabilnost farme. Da bi se sačuvala optimalna reproduktivna učinkovitost, predložene su različite moguće strategije i terapijski pristupi za krave s CE-om, često s kontradiktornim rezultatima. Iz tog je razloga istraživanje novih načina liječenja CE-a ekonomski bitno. Cilj ove studije bio je ispitati učinkovitost tri različita terapijska protokola na postotak kliničkog izlječenja CE-a te poboljšanje reproduktivne učinkovitosti. Krave ($n=42$), na 21.-38. dan laktacije (DIM), s CE-om raspoređene su u tri terapijske skupine; **PGF**: krave ($n=19$) su sistematski liječene s dvije doze d-kloprostenola, sintetičkog analoga $PGF_{2\alpha}$ 14-dnevni interval; **CEFAX**: krave ($n=10$) su primale intrauterinu infuziju kombinacije antibiotika cefacetrila i rifaksimina; **NAX**: krave ($n=13$) su primale sistemsku terapiju s ceftiofur kristaliničnom slobodnom kiselinom (CCFA). Trideset i šest ($n=36$) krava bez CE-a (zdrava skupina: **HE**) uključeno je kao kontrolna skupina. Sve krave su ponovno klinički pregledane nakon kraja protokola liječenja. Postotak kliničkog izlječenja iznosio

je 73,7 %, 80 % i 69,2 % u PGF, CEFAX, odnosno NAX skupini ($P>0,05$). HE skupina imala je značajno kraći interval između teljenja do prvog osjemenjivanja u usporedbi s CEFAX i PGF skupinama ($P<0,05$), no razlika nije bila značajna s NAX skupinom. Srednji interval od teljenja do osjemenjivanja za oplodnju (CFI) bio je nešto veći u tri terapijske skupine u usporedbi s HE skupinom, ali razlika nije bila značajna ($P>0,05$). CEFAX protokol rezultirao je kraćim, ali ne statistički značajnim CFI u usporedbi s PGF i NAX protokolima. Indeks osjemenjivanja po koncepciji bio je nešto niži (1,7) u CEFAX skupini u usporedbi s HE (1,75), PGF (1,84) i NAX (2,23) skupinama, međutim razlika nije bila značajna između sve četiri skupine. Postotak prvog uspješnog osjemenjivanja i postotak koncepcije na 105. DIM nisu se statistički razlikovale među terapijskim skupinama. Premda razlika nije bila značajna, CEFAX protokol imao je nešto bolji postotak izlječenja za CE, smanjujući broj osjemenjivanja po koncepciji i potičući ponovnu aktivnost jajnika nakon teljenja. Validacija ovog otkrića na većem krdu poboljšat će točnost ovih rezultata.

Ključne riječi: klinički endometritis, liječenje, postotak izlječenja, reproduktivna učinkovitost