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Randomized clinical trial of intrauterine cephapirin infusion in dairy cows for the treatment of purulent vaginal discharge and cytological endometritis

J. Denis-Robichaud[1] and J. Dubuc[2]
Faculté de médecine vétérinaire, Université de Montréal, C.P. 5000, Saint-Hyacinthe, Québec, J2S 7C6, Canada

ABSTRACT

The objectives of this study were to quantify the effect of an intrauterine infusion of cephapirin on reproductive performance at first service of postpartum dairy cows affected by purulent vaginal discharge (PVD) and cytological endometritis (ENDO) using different diagnostic strategies, and to determine if the presence of prolonged anovulation would influence the magnitude of treatment benefit. In total, 2,259 Holstein cows in 28 herds were enrolled in a randomized clinical trial. At 35 (±7) days in milk (DIM), cows were diagnosed with PVD using the Metricheck device (Simcro, Hamilton, New Zealand), with cytological endometritis using endometrial cytology (ENDO-CYTO), and with cytological endometritis using leukocyte esterase (ENDO-LE). Regardless of reproductive tract disease status, cows were randomly assigned to receive an intrauterine cephapirin infusion or to not be treated. Serum progesterone was measured at 35 and 49 (±7) DIM (14 d apart); cows were considered to have prolonged anovulation if progesterone was <1 ng/mL at both times. Reproductive events of cows were collected until 200 DIM. Statistical analyses were conducted using multivariable mixed logistic regression models. Intrauterine cephapirin treatment was associated with an increased first-service pregnancy risk in cows diagnosed with PVD (no treatment: 15.4%; treatment: 31.4%), ENDO-CYTO (no treatment: 16.2%, treatment: 24.4%), and ENDO-LE (no treatment: 15.8%; treatment: 25.1%), but not in cows unaffected by any form of reproductive tract disease (no treatment: 34.8%; treatment: 32.6%). Cephapirin treatment was also associated with an increased first-service reproductive performance in cows affected simultaneously by both PVD and ENDO-CYTO (no treatment: 8.7%; treatment: 23.4%). The effect of cephapirin treatment in anovular cows (no treatment: 21.0%; treatment: 26.4%) was numerically lower than in cyclic cows (no treatment: 22.7%; treatment: 34.1%). Overall, an intrauterine infusion of cephapirin improved first-service pregnancy risk in cows with postpartum reproductive tract disease and this effect was influenced by postpartum anovulation status.
Key words: dairy cow, treatment, endometritis, cephapirin

INTRODUCTION

Purulent vaginal discharge (**PVD**) and cytological endometritis (**ENDO**) are associated with impaired subsequent reproductive performance in postpartum dairy cows (LeBlanc et al., 2002a; Gilbert et al., 2005; Dubuc et al., 2010). The use of an intrauterine infusion of cephapirin is approved in Canada (Merck Animal Health, Montréal, Canada) and other countries for the treatment of PVD. Intrauterine cephapirin infusion has been shown by multiple studies to improve reproductive performance of dairy cows with PVD (LeBlanc et al., 2002b; Runciman et al., 2008), but little data are available for cows with ENDO (Kasimanickam et al., 2005). Interestingly, no studies have diagnosed and simultaneously reported PVD and ENDO when investigating the efficacy of an intrauterine cephapirin infusion. Using such an approach could provide more insight into the benefit of performing reproductive tract disease surveillance in dairy herds and on the benefit of treating affected cows.

Reproductive tract disease diagnostic tools such as the Metricheck (Simcro, Hamilton, New Zealand; McDougall et al., 2007; Dubuc et al., 2010), vaginoscope (LeBlanc et al., 2002a; Runciman et al., 2009), endometrial cytobrush (Kasimanickam et al., 2004; Dubuc et al., 2010), and endometrial leukocyte esterase (**LE**; Cheong et al., 2012, Couto et al., 2013) tests have been shown to be useful for the identification of cows with poorer subsequent reproductive performance. However, most of these studies evaluated only the association between one form of disease (PVD or ENDO) and subsequent reproductive performance. A recent study determined that the best pair of diagnostic criteria

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[1]Current address: Department of Population Medicine, University of Guelph, Guelph, Ontario, N1G 2W1, Canada.
[2]Corresponding author: Jocelyn.dubuc@umontreal.ca

when using the Metricheck and cytobrush techniques simultaneously was ≥4 (purulent or worse vaginal discharge; PVD) and ≥6% polymorphonuclear cells (**ENDO-CYTO**), respectively (Denis-Robichaud and Dubuc, 2015). Similarly, in the same report, the optimal pair of diagnostic criteria when using the Metricheck and leukocyte esterase techniques was ≥4 (purulent or worse vaginal discharge; PVD) and ≥1 (small amounts of leukocytes; **ENDO-LE**), respectively. The diagnostic performance of using these tests was reported, but it remains unclear at this time whether a treatment with intrauterine cephapirin infusion of cows diagnosed with PVD, ENDO-CYTO, or ENDO-LE using these strategies would improve their subsequent reproductive performance.

Although the use of intrauterine cephapirin therapy has been shown to be beneficial for cows with PVD (LeBlanc et al., 2002b; Runciman et al., 2008), only one study has investigated the effect of having or not a corpus luteum at the time of infusion (as a proxy for identification of anovular cows; LeBlanc et al., 2002b). It seems intuitive that the positive effect of cephapirin treatment on cows affected by PVD, ENDO-CYTO, or ENDO-LE may be modulated by ovulatory status. Prolonged postpartum anovulation has been associated with poorer reproductive performance (Walsh et al., 2007; Galvão et al., 2010; Dubuc et al., 2012) and the positive effect of intrauterine cephapirin in these cows could be influenced by it. A recent study reported that prolonged anovulation and cytological endometritis have additive detrimental effects on subsequent reproductive performance of cows (Vieira-Neto et al., 2014). Unfortunately, it remains unclear whether the presence of prolonged anovulation reduces the benefit of cephapirin intrauterine infusion in cows with PVD or ENDO.

Therefore, the first objective of this study was to quantify the effect of an intrauterine infusion of cephapirin on reproductive performance at first service in postpartum dairy cows affected by PVD, ENDO-CYTO, or ENDO-LE. The second objective was to determine if the presence of a prolonged anovulation period would influence the magnitude of the benefit from intrauterine cephapirin therapy.

MATERIALS AND METHODS

Holstein cows from 28 commercial dairy herds were enrolled in a randomized clinical trial conducted between October 2011 and December 2013 (26 herds were enrolled in the first year and 2 were enrolled in the second year of farm data collection). Herds were selected by convenience based on being within a 250-km radius of St-Hyacinthe (Québec, Canada), on having a computerized record system, and on using an ovulation synchronization protocol (Double-Ovsynch or Presynch-Ovsynch; systematic use of the same protocol within herd) to synchronize the first service of all cows around 70 DIM. Herd size ranged from 40 to 600 cows with a median of 91 cows. In total, 22 herds were housed in tiestall barns and 6 herds were housed in freestall barns (milking parlor). All cows that calved in these herds during the study period and that were bred at least once before 100 DIM were enrolled in the trial. Reproductive performance of these cows was recorded until 200 DIM. All herds used exclusively AI for breeding. Pregnancy diagnosis was performed by transrectal palpation between 33 and 47 d after insemination. Each cow could only be enrolled once in the study. The estimated sample size needed for this study was 2,344 cows. This sample size was planned to identify a difference of 10% in pregnancy risk at first service between treated (30%) and untreated (20%) cows with 95% confidence and 80% power (Dohoo et al., 2009) when expecting a disease prevalence of 25%.

Farms were visited biweekly (every 14 d) by an animal health technician and a veterinarian. Cows were examined for PVD, ENDO-CYTO, and ENDO-LE at 35 (±7) DIM. Purulent vaginal discharge was diagnosed first using vaginal discharge score assessed with the Metricheck device (0 = no discharge, 1 = clear mucus, 2 = mucus with flecks of pus, 3 = mucopurulent discharge, 4 = purulent discharge or 5 = foul smelling discharge; McDougall et al., 2007). Diagnostic of ENDO-CYTO was done using a cytobrush technique (endometrial cytology) adapted for use in cattle (Kasimanickam et al., 2004; Dubuc et al., 2010) and diagnostic of ENDO-LE was done using an LE technique (Couto et al., 2013). Immediately after collection, the cytobrush was rolled on a microscope glass slide to obtain a smear. After that, the cytobrush was placed in an individual 3-mL glass vial containing 1 mL of 0.9% saline (NaCl 0.9% Irrigation, Baxter Corp., Mississauga, ON, Canada). The microscope slides were stained within 12 h of collection with a modified Wright-Giemsa stain (Hema3; Biochemical Sciences, Swedesboro, NJ) and glass coverslips were applied when dry as previously described (Dubuc et al., 2010). The percentage of PMNL on these slides was determined using a microscope (400× magnification) and slides were read by 2 observers (an animal health technician and a veterinarian). Two hundred cells (PMNL and endometrial cells) were counted on each slide. Slide readers were blinded to on-farm findings and treatment allocation. Within 12 h of collection, the individual vial containing the cytobrush was shaken for 10 s and a drop of the solution was put on a commercial LE test strip (Multistix 10 SG; Bayer Corporation, Elkart, IN) using a pipette. Because of material availability, LE testing only began in December 2011 even though farm