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Randomized, controlled clinical trial on the efficacy of nonsteroidal antiinflammatory drugs for the treatment of acute puerperal metritis in dairy cows

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ABSTRACT

The objective of this study was to assess the efficacy of ketoprofen compared with ceftiofur hydrochloride for the treatment of acute puerperal metritis (APM). Specifically, we set out to compare the incidence of extended treatment (extT) between treatment groups, to determine the prevalence of purulent vaginal discharge (PVD) and milk yield on the first 3 milk tests postpartum, and to analyze reproductive performance of cows treated with ketoprofen or ceftiofur. Cows with rectal temperature ≥39.5°C and reddish-brown fetid vaginal discharge within the first 10 d in milk (DIM) were diagnosed with APM. Day of enrollment and first day of treatment was considered study day 1. Rectal temperature was recorded daily until study day 7. A total of 610 dairy cows with APM were enrolled in this randomized clinical trial. Cows meeting the inclusion criteria were allocated to treatment with ketoprofen (3 mg/kg of body weight, n = 300) or treatment with ceftiofur (1 mg/kg of body weight, n = 310) on study days 1, 2, and 3. Cows that showed rectal temperature ≥39.5°C between study days 4 and 7 received an extT with ceftiofur for 3 (ketoprofen group) or 2 (ceftiofur group) more days. Cows were examined with the Metricheck device (Simcro, Hamilton, New Zealand) between DIM 21 and 40, and vaginal discharge was categorized on a 5-point scale according to the presence of pus. Cows with a score ≥2 were classified as having PVD. Fifty-two cows (35 from ketoprofen group, 17 from ceftiofur group) were excluded from analysis due to missing protocol compliance (n = 37) or concurrent disease (n = 15). Cows treated with ketoprofen were more likely to have an extT than cows treated with ceftiofur (61 vs. 32%). Prevalence of PVD did not differ between the 2 treatment groups (ketoprofen, 56%; ceftiofur, 53%). Cows, however, that needed an extT after the initial 3-d treatment were more likely to develop PVD than cows without extT (64 vs. 46%). Treatment group did not affect milk yield (ketoprofen group, 35.5 ± 0.4 kg; ceftiofur group, 35.2 ± 0.3 kg), first artificial insemination pregnancy risk (ketoprofen group, 20% vs. ceftiofur group, 25%), median days to first artificial insemination [ketoprofen group, 73 d, 95% confidence interval (CI): 70–75 d vs. ceftiofur group, 75 d, 95% CI: 72–76 d] and median days to pregnancy (ketoprofen group, 144 d, 95% CI: 132–158 d vs. ceftiofur group, 133 d, 95% CI: 119–153 d). These results indicate that although cows initially treated with ketoprofen were more likely to receive extT, fewer doses of ceftiofur (1.83) were required compared with cows initially treated with ceftiofur (3.63). Moreover, the prevalence of PVD was not increased and milk yield and reproductive performance were not negatively affected by the initial treatment with ketoprofen.

Key words: acute puerperal metritis, animal health, antibiotic, nonsteroidal antiinflammatory drug (NSAID), reproduction

INTRODUCTION

Acute puerperal metritis (**APM**) is a common disease in early postpartum dairy cows (Chapinal et al., 2011; Sannmann et al., 2013b; Lima et al., 2014). Diagnosis of APM is based on reddish-brown fetid watery discharge and a rectal temperature ≥39.5°C within the first 21 DIM (Sheldon et al., 2006). Cows with APM have signs of systemic illness, are at greater risk of an impaired reproductive performance, are more likely to be culled, and have a greater risk of reduced milk production in comparison to healthy cows (Fourichon et al., 2000; Sheldon et al., 2006; Wittrock et al., 2011). Moreover, APM is a painful disease, and the pain response is particularly obvious during transrectal palpation of the uterus (Stojkov et al., 2015). In consequence, animal welfare as well as economic reasons illustrate the need of an effective treatment.

Different aerobic and anaerobic bacteria can be found in the infected uterus including *Escherichia coli*,

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Trueperella pyogenes, Prevotella spp., *Fusobacterium necrophorum*, *Fusobacterium nucleatum*, *Mannheimia haemolytica*, *Staphylococcus* spp., and *Streptococcus* spp. (Sheldon, 2004; Williams et al., 2005; Santos et al., 2011). Because of this wide range of pathogens, the suggestion to use antimicrobials with broad-spectrum activity as the preferred treatment is reasonable (Lima et al., 2014). Therefore, APM is commonly treated with third-generation cephalosporins (Machado et al., 2014). Another reason for the widespread use of ceftiofur administered parenterally is the 0-d withdrawal time for milk, resulting in a major financial incentive for using it (Grove-White and Murray, 2009; Scientific Advisory Group on Antimicrobials of the Committee for Medicinal Products for Veterinary Use, 2009; Lima et al., 2014). Moreover, the choice of other antimicrobials approved for the therapy of APM is limited. However, third-generation cephalosporins are very important antimicrobials for severe infections in humans, and their use in food-producing animals could potentially lead to an increased prevalence of resistance (Scientific Advisory Group on Antimicrobials of the Committee for Medicinal Products for Veterinary Use, 2009). Because antibiotic resistance is recognized as a top public health challenge facing the 21st century (Thomson et al., 2004), prudent use of antimicrobials and evaluation of alternative therapies are necessary.

In a clinical trial involving 1,023 cows, McLaughlin et al. (2012) showed self-cure of 55.3% in cows with APM not receiving antibiotic treatment compared with a cure of 74.3% of cows with APM treated with the long-acting formulation of ceftiofur (ceftiofur crystalline free acid sterile suspension) twice. An unspecified number of cows with abnormal clinical signs (e.g., dehydration, anorexia, weakness, or severe depression) received supportive therapy. The results indicated that more than half the cows from the control group self-recovered. Moreover, Sannmann et al. (2013b) showed no negative effect on clinical cure, milk yield, serum haptoglobin concentration, and subsequent uterine health when cows with APM within the first 5 DIM were left untreated. However, animal welfare has to be considered in cows without any treatment with regard to visceral pain of the uterus and systemic signs of illness (Sheldon et al., 2006; Stojkov et al., 2015).

Nonsteroidal antiinflammatory drugs (**NSAID**) have been described as a supportive treatment of APM in addition to antibiotics (Amiridis et al., 2001; Drillich et al., 2007). These drugs have analgesic, antiinflammatory, antipyretic, and antiendotoxic effects and thus can increase animal health and well-being (Fitzpatrick et al., 2004; Laven et al., 2012). Ketoprofen, an NSAID with 0-d withdrawal time in milk, was administered by Newby et al. (2013) after surgical correction of a left displaced abomasum to reduce pain, increase appetite, and increase milk production, and it has been approved for use in lactating cows in Europe. Antiinflammatory and analgesic effects of NSAID in combination with a remarkable self-cure of APM make it plausible to study the efficacy of ketoprofen in treatment of APM.

Therefore, the objective of this study was to evaluate if treating APM with ketoprofen is efficacious. Specifically, we set out to compare the incidence of extended treatment (**extT**) in cows with APM treated with ceftiofur or ketoprofen, to determine the prevalence of purulent vaginal discharge (**PVD**) between 21 and 40 DIM, the milk yield on the first 3 postpartum DHI tests, and to analyze reproductive performance (time to first AI, first AI pregnancy risk, and time to pregnancy) of cows treated with ketoprofen or ceftiofur.

MATERIALS AND METHODS

The experiment was conducted as a multisite completely randomized design. An a priori sample size calculation was conducted for the 2 main outcome variables: incidence of extT and first AI pregnancy risk.

For the comparison of the incidence of extT, Fisher's exact test for 2 independent groups was applied using G*Power (version 3.1.5, University of Düsseldorf). We hypothesized that the incidence of extT would differ and that cows treated with ketoprofen would be more likely to need an extT than cows treated with ceftiofur. Our assumption for differences in incidence of extT was based on a previous study (McLaughlin et al., 2012), which described clinical cure of 74.3 and 55.3% for cows treated with ceftiofur and untreated control cows, respectively. Using $\alpha = 0.05$, $\beta = 0.05$, and a 2-tailed study design, a sample size of 155 cows per treatment group was necessary to verify our hypothesis.

We hypothesized that the treatment group would not affect first AI pregnancy risk. A first AI pregnancy risk of cows that previously suffered from metritis of 38% was assumed (Santos et al., 2010). Sample size calculation was based on a noninferiority study design, with a 10% maximum difference in first AI pregnancy risk between treatment groups required to declare noninferiority of a treatment with ketoprofen (Sealed Envelope Ltd., London, UK). A total of 292 cows per treatment group were estimated to be required to demonstrate noninferiority, assuming $\alpha = 0.05$ and $\beta = 0.20$.

Farms and Cows

The experiment was conducted on 6 commercial dairy farms in the northeastern part of Germany between June 2013 and February 2015. Participating farms were recruited based on convenience. Herd size ranged from