



EFFECT OF INTRAUTERINE INFUSION OF TWO CEPHALOSPORINS, CEFTAZIDIME AND CEPHAPIRIN, ON UTERINE BACTERIAL LOAD AND UTERINE HORN DIAMETER IN BOVINE SUBCLINICAL ENDOMETRITIS

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Summary

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This study aimed to evaluate the effect of intrauterine infusion of ceftazidime and cephapirin on uterine bacterial load and uterine horn diameter in bovine subclinical endometritis. At 7–8 weeks postpartum, a total of 122 cows suffering from subclinical endometritis were divided into three groups. Group I cows were intrauterinely (IU) infused with 2 g ceftazidime diluted with 50 mL saline; group II cows were IU infused with 2 g cephapirin diluted with 50 mL saline; and group III cows were kept as untreated control. Vaginal examination, ultrasonography and bacterial examination were done before treatment programme and later repeated twice at 10-day intervals. *Staphylococcus* spp., *Klebsiella* spp., *Streptococcus* spp., *Escherichia coli* and *Proteus* spp. were isolated. After the end of the treatment programme, proportions of cows infected with *Staphylococcus* spp. and *Streptococcus* spp. were significantly ($P<0.05$) decreased in ceftazidime and cephapirin groups. However, proportions of cows infected with *Escherichia coli* were significantly ($P<0.05$) decreased in the ceftazidime group only. Uterine bacterial loads in ceftazidime and cephapirin groups were significantly decreased ($P<0.05$). Mean uterine horn diameters in ceftazidime group (2.44 ± 0.03 cm) became significantly lower ($P<0.05$) than those in cephapirin (2.70 ± 0.04 cm) and control (3.06 ± 0.06 cm) groups. Conception rate in ceftazidime group (80.95%) was significantly ($P<0.05$) higher than rates recorded in cephapirin (64.00%) and control (26.67%) groups. In conclusion, ceftazidime and cephapirin decreased uterine bacterial load. Moreover, ceftazidime significantly reduced uterine horn diameter compared to the other groups and was associated with significantly higher conception rate. Thus, ceftazidime is recommended for treatment of subclinical endometritis in dairy cows.

Key words: bacterial load, conception rate, dairy cows

INTRODUCTION

Uterine health status in dairy cows is an important factor for maintenance of good reproductive performance (Yu *et al.*, 2016). The healthy uterine environment allows sperm cells to successfully pass the reproductive system to reach the fertilisation site and allow the foetus to develop in a favourable environment (Cheong *et al.*, 2017). Intrauterine bacterial infection impair reproductive performance in dairy cows. During the infection, the pathogen adheres to the mucosa, colonisation, epithelial penetration and release of bacterial toxins that lead to uterine disease as endometritis occur (Azawi *et al.*, 2008; de Boer *et al.*, 2015). The presence of pathogenic bacteria in the uterine cavity leads to intrauterine accumulation of echogenic fluid that may lead to increased uterine size (Piersanti *et al.*, 2019).

Subclinical endometritis is one of the problems affecting the reproductive status of dairy cows. It is an inflammatory condition of the uterus in the absence of clinical signs (Arias *et al.*, 2018). To overcome this problem, several treatments have been used, among which a wide range of antibiotics and hormones. Intrauterine treatment with antibiotics has been widely used to reduce the effect of uterine disease on fertility (Wagener *et al.*, 2017). Cephalixin is an antibiotic from the first generation cephalosporins while ceftazidime: from the third generation. They have broad spectrum activity and are widely used in clinical practice (Kasimanickam *et al.* 2005; de Santana *et al.*, 2019).

Therefore, the objectives of this study were to determine the effects of ceftazidime and cephalixin on uterine bacterial load and uterine horn diameter in bovine subclinical endometritis.

MATERIALS AND METHODS

Animals

The present study was carried out from March 2017 to February 2019. A total number of 122 cows aged from 3–5 years suffering from subclinical endometritis at 7–8 weeks postpartum were used. Cows without abnormal vaginal discharge and having $\geq 5\%$ polymorphonuclear cells (PMN) were included in the study. Animals were housed outdoors in open hygienic yards; were fed grass silage, concentrate and hay. They were vaccinated against Lumpy skin disease, foot and mouth disease and rift valley fever. First ultrasonography and bacteriological examination were done before the treatment programme then repeated twice at 10-day intervals.

Vaginal examination

Cows were inspected for the presence of fresh discharge on the vulva, perineum or tail, and then the animals were examined through the vagina. The cow's vulva was thoroughly cleaned with a dry paper towel, a lubricated vaginal speculum was inserted into the vagina far enough to enable visualisation of the external cervical os for assessment of discharge.

Cytological examination

Uterine samples were taken using sterilised transcervical guarded swabs. The swab was rolled on a clean glass slide and left to dry. The slide was stained by Rapi-Diff II Stain (Diff-Quick). Cytological evaluations was performed by counting a minimum of 100 cells at 400 \times and 1000 \times magnification under microscope to determine PMN cells percentage. To evaluate

subclinical endometritis, 5% PMN was considered as cut-off value (Fuentes *et al.* 2017).

Ultrasonography

Ultrasonography was performed using a portable real-time B-mode transrectal ultrasound scanner (SonoScape, Model: M12, SonoScape Medical Corp, Guangdong, China). Reproductive tract measurements included uterine horn size at the base of the horn; ovarian status and presence of fluid in the uterus (Senosy *et al.*, 2009). Means of right and left uterine horn measurements were calculated before the treatment programme and twice later at 10-day intervals.

Bacteriological examination

Using the collected swab sample sticks, streaking method was used for bacteriological examination. Isolation was made from each swab sample on nutrient agar plates. The plates were incubated aerobically at 37 °C for 24 hours. The isolates were subcultured to get pure isolates (Shinkafi & Dauda, 2013). Isolated colonies were cultured aerobically at 37 °C for 24–48 hours on blood agar and MacConkey agar. According to Barrow & Feltham (1993), bacteria were identified on the basis of the characteristics of the colony, Gram staining, morphology, haemolysis, catalase, coagulase, mannitol, oxidase, urease, Triple-sugar iron agar tests and motility test.

Bacterial load was determined by standard plate count method using ten-fold serial dilutions. One milliliter of each dilution was transferred to nutrient agar plate and the liquid was spread thoroughly and evenly over the surface of the plate using a sterile disposable spreader. Agar plates were incubated at 37 °C for 24–48 hours. Colonies of the plate having 30 to

300 colonies were counted. Colony-forming units per milliliter (CFU/mL) were calculated by multiplying number of colonies with the dilution factor (Cain *et al.*, 2013; Kumar *et al.*, 2013).

Treatment protocols

After first examination, cows were divided into three groups. Group I cows were intrauterinely (IU) infused with 2 g ceftazidime diluted with 50 mL saline; group II cows were IU infused with 2 g cephalixin diluted with 50 mL saline; and group III cows were kept as untreated control. Another treatment was given 10–11 days later in all treatment groups.

Evaluation of conception rate

The cows were inseminated artificially at first estrus after end of treatment programme. The conception rate was calculated as total number of pregnant cows divided by total number of inseminated cows multiplied by 100 (Scheffers *et al.*, 2010).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 22.0 (SPSS for Windows 22.0, Inc., Chicago, IL, USA). Chi-square test was used for comparison of proportions of cows positive for isolated microorganisms and conception rate in different treatment groups. Duncan's test was performed for comparing mean values of bacterial counts and uterine horn diameter within groups and between the groups. Data are represented in mean±SEM; P<0.05 was considered to be significant.

RESULTS

One hundred and twenty two dairy cows suffering from subclinical endometritis

were included in this study. Isolation and identification before treatment revealed that *Staphylococcus* spp, *Klebsiella* spp., *Streptococcus* spp, *Escherichia coli* and *Proteus* spp were isolated from 34.43%, 18.03%, 29.51%, 21.31% and 13.11% of cows respectively. After the end of treatment programme, proportions of cows infected with *Staphylococcus* spp. and *Streptococcus* spp. were significantly ($P<0.05$) decreased in ceftazidime- and cephapirin-treated groups. However, proportion of cows infected with *Escherichia coli* was significantly ($P<0.05$) decreased in ceftazidime group only (Table 1). Average total bacterial count performed for uterine samples, before treatment ranged

from 40.50×10^7 to 47.70×10^7 CFU/mL. These values were significantly decreased after treatment by ceftazidime and cephapirin. At second examination, mean bacterial counts in ceftazidime and cephapirin groups (5.82×10^4 and 38.00×10^4 CFU/mL, respectively) were significantly lower ($P<0.05$) than control group value (39.50×10^7 CFU/mL). Moreover, at third examination, mean bacterial count in ceftazidime and cephapirin groups (0.65×10^4 and 1.77×10^4 CFU/mL, respectively) were significantly lower ($P<0.05$) compared to the control group (39.20×10^7 CFU/mL) (Table 2).

Ultrasound examination revealed that at second examination, the mean uterine

Table 1. Number and proportion of cows positive for isolated microorganisms in different treatment groups

Isolated microorganisms	Ceftazidime (n=42)	Cephapirin (n=50)	Control (n=30)	Total (n=122)	P value
Before treatment					
<i>Staphylococcus</i> spp	16 (38.10%)	14 (28.00%)	12 (40.00%)	42 (34.43%)	0.45
<i>Klebsiella</i> spp	8 (19.05%)	8 (16.00%)	6 (20.00%)	22 (18.03%)	0.88
<i>Streptococcus</i> spp	10 (23.81%)	16 (32.00%)	10 (33.33%)	36 (29.51%)	0.60
<i>Escherichia coli</i>	10 (23.81%)	6 (12.00%)	10 (33.33%)	26 (21.31%)	0.07
<i>Proteus</i> spp	6 (14.29%)	6 (12.00%)	4 (13.33%)	16 (13.11%)	0.95
After treatment					
<i>Staphylococcus</i> spp	3 (7.14%) ^a	3 (6.00%) ^a	11 (36.67%)	17 (13.93%)	<0.00
<i>Klebsiella</i> spp	4 (9.52%)	5 (10.00%)	5 (16.67%)	14 (11.48%)	0.59
<i>Streptococcus</i> spp	2 (2.38%) ^a	3 (6.00%) ^a	8 (26.67%)	12 (9.84%)	<0.00
<i>Escherichia coli</i>	2 (4.76%) ^a	2 (4.00%)	8 (26.67%)	12 (9.84%)	<0.00
<i>Proteus</i> spp	4 (9.52%)	2 (4.00%)	3 (10.00%)	9 (7.38%)	0.49

$P<0.05$ within rows between different groups; ^a significant difference ($P<0.05$) for cows positive for the same isolated microorganism before and after treatment within columns.

Table 2. Uterine bacterial count (CFU/mL) in different treatment groups (mean±SEM)

Treatment groups	N	First examination	Second examination	Third examination
Ceftazidime	42	$47.70 \pm 10.50 (\times 10^7)^{aA}$	$5.82 \pm 0.26 (\times 10^4)^{aB}$	$0.65 \pm 0.19 (\times 10^4)^{aB}$
Cephapirin	50	$43.00 \pm 9.04 (\times 10^7)^{aA}$	$38.0 \pm 4.27 (\times 10^4)^{aB}$	$1.77 \pm 0.34 (\times 10^4)^{aB}$
Control	30	$40.50 \pm 6.69 (\times 10^7)^{aA}$	$39.5 \pm 5.33 (\times 10^7)^{bA}$	$39.20 \pm 11.00 (\times 10^7)^{bA}$

The different superscript small letters between different groups within columns and capital letters between different stages of examination within rows means significant difference at $P<0.05$.

horn diameter in the ceftazidime and cephalirin groups (2.81 and 2.97 cm respectively) were significantly lower ($P<0.05$) than in control cows (3.09 cm). However, at third examination, the mean uterine horn diameter in ceftazidime group (2.44 cm) was significantly lower ($P<0.05$) than both cephalirin and control (2.70 and 3.06 cm respectively) groups (Table 3; Fig. 1 and 2).

Artificial insemination was performed at first estrus after the end of treatment. It was observed that conception rate in ceftazidime (80.95%) group was significantly higher ($P<0.05$) than those in cephalirin-

treated (64.00%) and untreated control (26.67%) groups (Table 4).

DISCUSSION

Bacterial contamination of the uterine cavity is common in cows and often leads to uterine diseases as endometritis (Sheldon *et al.*, 2008). The prevalence rates of subclinical endometritis and purulent vaginal discharge were increased in cows with persistent uterine infections at 5–7 weeks post-partum (Ghanem *et al.*, 2014). Bacteriological examination in the present study showed that *Staphylococcus* spp,

Table 3. Uterine horn diameter (cm) in different treatment groups (mean±SEM)

Treatment groups	N	First examination	Second examination	Third examination
Ceftazidime	42	3.18±0.03 ^{aA}	2.81±0.02 ^{aB}	2.44±0.03 ^{aC}
Cephalirin	50	3.20±0.02 ^{aA}	2.97±0.07 ^{bB}	2.70±0.04 ^{bC}
Control	30	3.16±0.02 ^{aA}	3.09±0.05 ^{cA}	3.06±0.06 ^{cA}

The different superscript small letters between different groups within columns and capital letters between different stages of examination within rows means significant difference at $P<0.05$.



Fig. 1. Ultrasonographic image of a transverse section of the uterine horn (6 MHz probe; depth of 111 mm) at first examination (before treatment). Uterine horn diameter: 32.5 mm; endometrium thickness: 12.2 mm.



Fig. 2. Ultrasonographic image of a transverse section of the uterine horn (6 MHz probe; depth of 111 mm) at third examination (after treatment). Uterine horn diameter: 23.7 mm; endometrium thickness: 6.1 mm.

Table 4. Conception rate in different treatment groups

Groups	N	1 st service	2 nd service	3 rd service	Total conception rate
Ceftazidime	42	57.14% (24/42)	44.44 % (8/18)	20.00 % (2/10)	80.95 % (34/42)
Cephapirin	50	32.00% (16/50)	41.18 % (14/34)	10.00 % (2/20)	64.00 % (32/50)
Control	30	0.00% (0/30)	13.33 % (4/30)	15.38 % (4/26)	26.67 % (8/30)
P-value		<0.00	0.02	0.74	<0.00

P<0.05 within columns between different groups indicates a significant difference.

Klebsiella spp., *Streptococcus* spp., *Escherichia coli* and *Proteus* spp. were isolated before treatment. In this context, Machado *et al.* (2018) reported that most prominent pathogens associated with uterine diseases were *Escherichia coli*, *Trueperella pyogenes* and *Fusobacterium necrophorum*. A previous study revealed that *E. coli* was the main bacterial risk factor for the occurrence of subclinical endometritis (Salah *et al.*, 2017). In contrast with this study, our study revealed that only 21.31% of cows were infected with *E. coli* versus 34.43% for *Staphylococcus* spp.

Systemic and local treatments have been used for endometritis. Among these treatments are antibiotics that decrease the number of pathogens in the uterine cavity and thus reduce infection, enhance local immune defense and facilitate the repair of the endometrium to return to normal uterine status faster (Lefebvre *et al.*, 2012; Wagener *et al.*, 2017). The bacterial growth density increases the risk for both clinical and subclinical endometritis in dairy cows (Prunner *et al.*, 2014). In our study before treatment, uterine bacterial load ranged from 40.50×10^7 to 47.70×10^7 CFU/mL. However, after treatment by cephalpirin, bacterial load was decreased from 43.00×10^7 to 1.77×10^4 CFU/mL. Moreover, proportions of cows infected with *Staphylococcus* spp. and *Streptococcus* spp. were significantly (P<0.05) decreased in ceftazidime and cephalpirin

groups. This result came in the same line with a previous study about subclinical endometritis in buffaloes which reported a positive effect on recovery, clearance of pathogenic bacteria after intrauterine treatment with cephalpirin (Nehru *et al.*, 2018). Ceftazidime as a third-generation cephalosporin is used to treat infections produced by Gram-positive and Gram-negative bacteria (Martínez-Moreno *et al.*, 2017). A previous study on treatment of urolithiasis reported that ceftazidime significantly reduced bacterial load on ureteral stent tissue (Wang *et al.*, 2016). In our study it reduced the uterine bacterial load from 47.70×10^7 to 0.65×10^4 CFU/mL at the third examination after the end of treatment.

Ultrasonography has been used as a method to diagnose subclinical endometritis based on the presence of intrauterine fluid and on the evaluation of uterine diameter (Arias *et al.*, 2018). Akhter *et al.* (2013) reported a reduction in accumulated fluid and uterine diameter after antibiotic treatment. In the present study, uterine horn diameters were significantly reduced from 3.20 to 2.70 cm after intrauterine infusion of cephalpirin. Moreover, using ceftazidime in the present study led to reduction of uterine horn diameter from 3.18 to 2.44 cm that became significantly lower than when cephalpirin was used. This reduction may be due to lower inflammatory levels similarly to a previous study reporting that ceftazidime reduced

pulmonary inflammatory levels after administration of *Klebsiella pneumoniae* to experimental guinea pig (Wei *et al.*, 2013).

Baez *et al.* (2016) revealed that there was a negative correlation between uterine size and fertility in dairy cows. Routine monitoring of the efficacy of reproductive programs is essential in dairy herds (Nishida *et al.* 2006). Unlike El-Rheem *et al.* (2019) who achieved lower conception rate after intrauterine antibiotic treatment, our findings revealed high conception rate after ceftazidime treatment. Kasimanickam *et al.* (2005) reported that cephalixin improved the reproductive performance of cows with subclinical endometritis. Furthermore, the total conception rate in ceftazidime group was significantly higher than those in cephalixin and control groups.

CONCLUSION

Intrauterine infusion of ceftazidime and cephalixin decreased uterine bacterial load. Moreover, ceftazidime significantly reduced uterine horn diameter more than other groups and resulted in significantly higher conception rate. Thus, ceftazidime is recommended for treatment of subclinical endometritis in dairy cows.

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