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Research Paper

The Effects of Flunixin Meglumine and Meloxicam on the Mucosal Immunity of the Uterus in Postpartum Cattle

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ABSTRACT

Introduction: During the transition period, dairy cows experience significant inflammatory immune responses that can act adversely affect the uterus. Modulation of the immune response and reduction of the negative effects of systemic inflammation after parturition may be achieved through the postpartum administration of non-steroidal anti-inflammatory drugs (NSAIDs). Therefore, the aim of this study was to investigate the effects of flunixin meglumine and meloxicam on local humoral immunity in the uterus of postpartum cows.

Materials & Methods: The study involved 60 cows that had undergone their second to fourth parturition. The animals were randomly divided into three groups. Treatment groups one and two received intravenous (IV) flunixin meglumine and meloxicam, respectively, on the 3rd and 8th days postpartum. The third group served as the control and received an IV injection of sterilized normal saline. Cervical mucus samples were collected from all animals on the 4th, 9th, and 15th days post-delivery. Uterine mucosal antibody titers against two primary pathogens, *Trueperella pyogenes* and *Escherichia coli*, were evaluated using an in-house enzyme-linked immunosorbent assay (ELISA). Additionally, serum antibacterial activity against these bacteria was assessed using the microdilution method.

Results: The antibacterial activity and mucosal antibody titers against *E. coli* revealed no statistically significant differences among the study groups. In contrast, the specific mucosal antibody titers against *T. pyogenes* increased during study period in both the control and flunixin-treated groups. Significant differences in mucosal antibody titers against *T. pyogenes* were observed between the meloxicam and flunixin groups on days 4 and 9 postpartum.

Conclusion: In conclusion, these findings suggest that neither treatment adversely effected uterine mucosal immunity. However, NSAID administration appeared to exert different effects on antibody titers against various pathogens. These differences may be related to variations in immune responses against target pathogens as well as differences in bacterial exposure levels within the environment. Therefore, veterinarians should consider farm management practices and environmental conditions when administering flunixin and meloxicam to postpartum dairy cows.

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1. Introduction

The dairy cows undergo significant physiological and immunological changes during the transition period, which are critical for delivery, colostrum secretion, and milk production [1]. These situation, along with decreased dry matter intake, lead to a negative energy balance and immunosuppression. Consequently, dairy cows are particularly susceptible to reproductive tract infections during the periparturient period [2]. Uterine infection commonly occurr following parturition in dairy cows due to the immunecompressed conditions and presence of bacterial contamination. Two bacterial species, *Trueperella pyogenes* and *Escherichia coli*, play significant roles in uterine inflammation and infection. For this reason, *E. coli* lipopolysaccharide (LPS) has been widely used to investigate the response of genital epithelial cells to bacterial contamination.

A variety of peptides and proteins secreted from epithelial cells of the genital tract possess non-specific antimicrobial properties and function as regulators of inflammation. Although the precise mechanisms regulating the secretion of antimicrobial peptides by endometrial epithelial cells remain unclear, cytokine stimulation is believed to play an important role. Immunoglobulins play a crucial role in preventing local infections by neutralizing invading bacteria, promoting phagocytosis, and activating complement activation pathways. The sequential appearance of IgM, IgA, and IgG in cervico-vaginal secretions following experimental challenge of the bovine uterus with *Campylobacter fetus* has previously been reported [3]. Evidence also suggests that the concentrations of different classes of immunoglobulins may vary among different regions of the genital tract. In cows with abnormal puerperium, both IgA and IgG concentrations increase rapidly in uterine fluids during the development of endometritis [4].

Administration of non-steroidal anti-inflammatory drugs (NSAIDs) could help regulate the immune response after postpartum and reduce the negative effects of postpartum inflammation [5]. NSAIDs exert their effects primarily through inhibition of cyclooxygenase (COX) enzymes. The inducible form of this enzyme, COX-2, is responsible for the production of prostaglandins involved in inflammation, fever, and pain. Consequently, NSAIDs are widely used for their antipyretic, analgesic, and anti-inflammatory properties [6]. Shwartz et al. (2009) evaluated the effects of flunixin treatment after calving and suggested that the uterine trauma and subsequent inflammation resulting from normal parturition could be alleviated through NSAID administration [7].

Meloxicam, as an NSAID that selectively inhibits cyclooxygenase-2 (COX-2), has been suggested as an effective method for alleviating inflammation [8]. In addition, meloxicam was mentioned as an analgesic drug [9] and has beneficial effects in the treatment of uterine prolapse [10]. Administration of meloxicam in combination with antibiotics for the treatment of mild to moderate clinical mastitis has been associated with improved treatment outcomes, higher conception rates following first artificial insemination, reduced inoculation rates, and an increased number of pregnant cows. Newby et al. (2017) reported that cows treated with flunixin meglumine after calving exhibited a higher incidence of retained placenta and, consequently, increased rates of clinical metritis and postpartum fever. Furthermore, these animals showed reduced milk production and an elevated risk of stillbirth, retained fetal membranes (RFM), and metritis [11]. Therefore, the present study was designed to evaluate the effects of flunixin meglumine and meloxicam on local uterine immunity in postpartum dairy cows.

2. Materials and Methods

The samples evaluated in this study were collected between August and September 2023. Holstein- Friesian cows from a dairy farm in Esfahan Province, Iran, were included in this study. A total of 60 cows that had undergone their second, third, and fourth parturitions were randomly assigned to three studied groups. Animals were excluded from the study if they experienced dystocia, twin birth, mastitis, lameness, retained placenta, or any other clinical disorder. In accordance with the study objectives, the initial inflammatory responses within the uterus were considered crucial for establishing immune responses and promoting tissue repair following parturition. Therefore, the timing of the first treatment, three days after parturition, selected to allow the necessary inflammatory phase to occur before intervention. Treatment group 1 received an intravenous (IV) injection of flunixin meglumine at a dose of 2.2 mg/kg was injected on the 3rd and 8th days post-delivery [11]. Treatment group 2 received an IV injection of meloxicam at a dose of 0.5 mg/kg on the same days after delivery [8]. Treatment group 3 served as the control group and received an IV injection of sterilized normal saline.

2.1. Sampling

Considering that the half-life of both drugs is less than 24 hours, sampling was performed 24 hours after each treatment. Cervical mucus samples were collected from the treated animals on days 4, 9, and 15 postpartum. Mucous from the external opening of the cervix was collect-

ed using a plastic uterine pipette attached to a syringe to create suction. The collected samples were transfered into 2-mL microtubes and homogenized with the same volume of phosphate buffered saline (PBS). The suspension was vortexed for 3 minutes and then centrifuged at 10,000 rpm for 20 minutes. The supernatant was collected and stored at -70 ˚C [12].

2.2. Preparation of bacterial antigens

The used *E. coli* and *T. pyogenes* strains used in this study were obtained from previously isolated bacterial stains in the Department of Microbiology, Faculty of Veterinary Medicine, Shahid Chmran University of Ahvaz, Iran. These strains had been previously characterized using biochemical properties. The bacterial isolates were cultured separately on blood agar medium enriched with 5% sheep blood and incubated at 37 ˚C for 24–48 hours. Suspensions of *E. coli* and *T. pyogenes* were prepared simultaneously, achieving concentrations of approximately 12×10^8 CFU/mL. Bacterial inactivation was achieved by incubating the bacterial strains in a 1% formalin solution for 24 hours at room temperature. Following removal of formalin by centrifugation, complete bacterial inactivation was confirmed by culture of the formalin-treated bacteria. The antigen solutions were then sonicated for ten cycles of 15 seconds each lasting and stored in a -20 ˚C.

2.3. Preparation of specific antibodies against *E. Coli* and *T. Pyogenes*

Polyclonal IgG antibodies specific for *E. coli* and *T. pyogenes* were purified from rabbit hyperimmune serum. Briefly, bacterial antigen concentration was adjusted to a turbidity equivalent to 4 McFarland standards. A suspension of 0.5 mL antigen was mixed with an equal volume of complete Freund's adjuvant and injected intramuscularly into the thigh muscles of two rabbits. Four booster immunizations were subsequently administered at 10-day intervals. Each booster consisted of 0.5 mL of bacterial suspensions adjusted to a turbidity of 2 McFarland and mixed with 0.5 mL of incomplete Freund's adjuvant. Antibody production was monitored using an indirect enzyme-linked immunosorbent assay (ELISA). Folowing confirmation of the appropriate antibody titers, blood samples were collected, and the hyperimmune sera were harvested. IgG purification of from hyperimmune serum was achieved according to the method described by Khosravi et al. (2021) using ion-exchange chromatography [13]. Briefly, hyperimmune sera were precipitated with 33% saturated ammonium sulfate. After centrifugation, the sediments were dialyzed against phosphate buffer (0.02 M, pH 7.2) for 48 hours. Ion- exchange chromatography was conducted using a DEAE-cellulose column. The resin powder was soaked in 0.02 M phosphate buffer solution (PBS) (pH 7.2) for 24 hours and then transferred to the column. The dialyzed solution was added to the column and incubated for 2 hours. The IgG fraction was eluted by adding 0.02 M PBS (pH 7.2). The purity and reactivity of the isolated antibodies were evaluated through respectively, dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and the ELISA, as described in the following section.

2.4. Evaluation of total antibody titer against *E. coli* and *T. pyogenes*

The mucosal antibody titer against *E. coli* and *T. pyogenes* were determined using an in-house indirect competitive ELISA. Initially, the concentrations and volumes of all reagents were optimized to facilitate competition between cattle antibodies present in cattle mucus samples and specific rabbit-derived antibodies. In addition to negative control samples, serial dilutions of the rabbit- specific antibodies, without mucus samples, were included as positive controls. The concentration of the sonicated bacterial antigens concentration was adjusted to 10 µg/mL in carbonate-bicarbonate coating buffer (pH=9.6), and 100 µL of the antigen solution was added to each well of the ELISA microplate. After incubation at 4 ˚C for 24 hours, the plates were washed three times with PBS containing 0.05% Tween 20 solution (PBS-T). Blocking step was performed by adding 250 µL of 4% skimmed milk to each well. In a separate plate, 10 µL of the mucus samples supernatant were diluted with 90 µL of PBS and then transferred to the antigen-coated wells. Subsequently, 20 µL of rabbit anti-*E. coli* IgG or rabbit anti-*T. pyogenes* IgG 150 µg/mL was added to each well, and the plate was incubated for 1 hour. After washing, 100 µL of horseradish peroxidase-conjugated anti-rabbit antibody was added to each well, and the plates were incubated at room temperature for an additional hour. After five washing steps, 75 µL of TMB solution was added to each well. The reaction was terminated after 10 minutes by adding 75 µL of 2 M sulfuric acid.

Optical density (OD) values were measured at 450 nm using an spectrophotometer (AccuReader, Taiwan). Rabbit anti-*E. coli* IgG and rabbit anti-*T. pyogenes* IgG at concentrations ranging from 32.5-300 µg/mL were used as positive controls. Protein concentrations in the analyzed mucus samples were determined using the Bradford method. Briefly, 20 µL of mucus sample, 80 µL of distilled water, and 100 µL of Bradford buffer

were mixed in the wells of a 96-well microplate. Additionally, six dilutions of bovine serum albumin (BSA) were prepared as standards. Finally, the OD values were measured at 600 nm using a spectrophotometer. Because an inverse relationship existed between the OD values obtained in the competitive ELISA and antibody titers; so, the results were normalized by subtracting each value from 1 and dividing by the corresponding protein volume.

2.5. Serum antibacterial effects

The antibacterial activity of cattle sera was evaluated using the microdilution method in sterile 96-well microplates. The *T. pyogenes* and *E. coli* strains were cultured, and a single colony from each strain was inoculated into nutrient broth media and incubated at 37 ˚C until it achieved a turbidity corresponding to the 0.5 McFarland standard. Each sample equal to 50 µL was combined with the same volume of the nutrient broth medium in the specified wells of the microplate. Subsequently, 50 µL of the bacterial suspension was added to each well. Initial OD values were measured at 600 nm using a spectrophotometer. The microplates were then incubated at 37 ˚C for 24 hours, after which the OD values were recorded as previously outlined. The interpretation of results involved calculating the bacterial growth in both the test and control wells [14]. Because of the inverse relationship between the obtained optical densities and the antibacterial activity of the mucus samples, the results were normalized by subtracting each value from 1 and dividing it by the corresponding protein volume.

2.6. Data analysis

Statistical analysis was conducted using of SPSS software version 23. Data were analyzed using two-way ANOVA. GraphPad Prism software, version 8 was utilized for graphical presentation of the results.

3. Results

The purification of IgG from the hyperimmune serum of rabbits immunized against *T. pyogenes* and *E. coli* was successfully performed using ion -exchange chromatography. The SDS-PAGE analysis revealed distinct protein bands in each lane of the gel, indicating the effective isolation of IgG (Figure 1A). The fractions containing purified antibodies were pooled, and the final concentrations were standardized to 300 µg/mL. Additionally, ELISA results indicated hyperimmunization of the treated rabbits (Figure 1B).

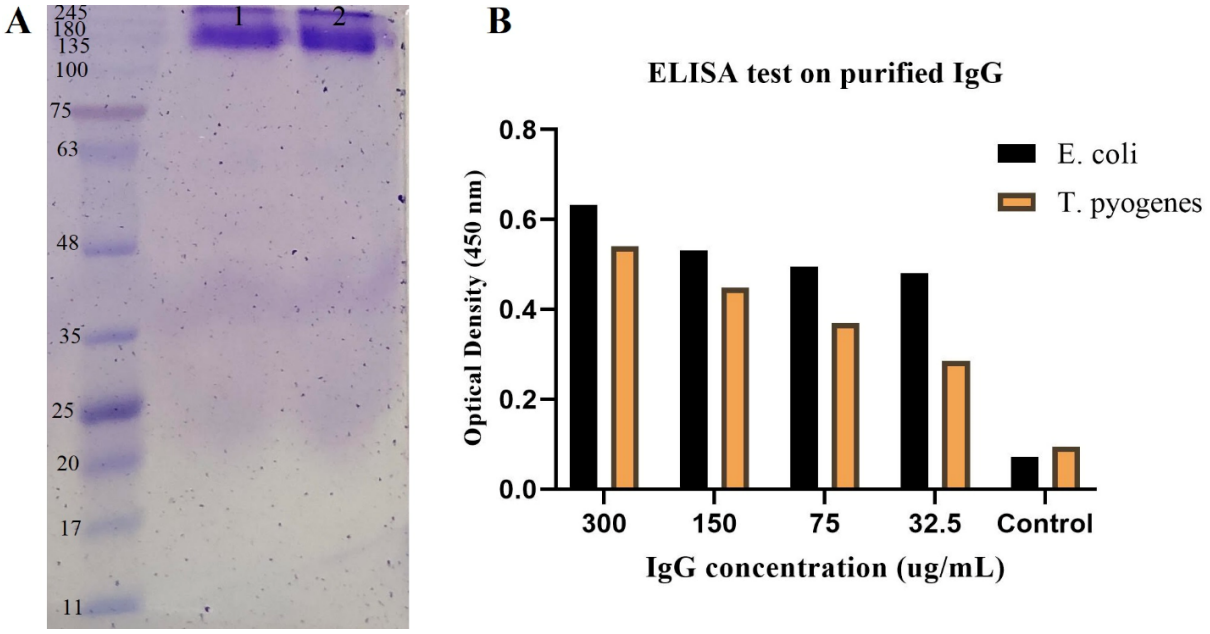

Figure 1. Purity and reactivity of IgG extracted from rabbit hyperimmune serum against *T. pyogenes* and *E. coli*

A) 1: Purified IgG against *T. pyogenes;* 2: Purified rabbit IgG against *E. coli;* B) The optical density obtained from the ELISA test at four concentrations of the purified IgG against *T. pyogenes* and *E. coli*

Note: The standard molecular weight proteins are indicated on the gel.

The mean mucosal antibody titers against *E. coli* and *T. pyogenes* are presented separately in Figure 2. The specific mucosal antibody titers against *E. coli* in the flunixin, meloxicam, and control groups showed no significant differences over time. Likewise, comparisons among groups on days 4, 9, and 15 postpartum indicated no statistically significant differences (Figure 2A).

The specific mucosal antibody titer against *T. pyogenes* showed a non-significant elevation over time in both the control and flunixin groups. In contrast, the meloxicam-treated group exhibited relatively constant titers on day 9, followed by a non-significant decrease in antibody titer observed on day 15. Comparisons of mucosal antibody titers against *T. pyogenes* revealed significant decrease between the meloxicam and flunixin groups on days 4 and 9 postpartum (P=0.199 and P=0.013, respectively) (Figure 2B). The antibacterial activity against *E. coli* revealed no statistically significant differences among the analyzed groups. However, the meloxicam-treated group exhibited significantly higher antibacterial activity against *T. pyogenes* on day 9 (P=0.008), compared with flunixin and control groups. Although higher antibacterial activity was also observed in the meloxicam group on the other sampling days, these differences weren't statistically significant (Figures 2C and 2D).

4. Discussion

The structure of the reproductive system serve as crucial mechanisms against infections that may occur during and after calving, thereby preventing pathogenic organisms from infiltrating the uterus. It is also noteworthy that all healthy animals typically harbor a significant bacterial population in the uterus following a normal parturition, however, uterine contamination post-calving is unavoidable. *E. coli* may play a main role in initiating the infectious process, and its detection several days after parturition is associated with an increased incidence of metritis and endometritis. Additionally, *T. pyogenes* has been identified in the uterine environment of cows suffering from metritis [15]. The treatment groups in the

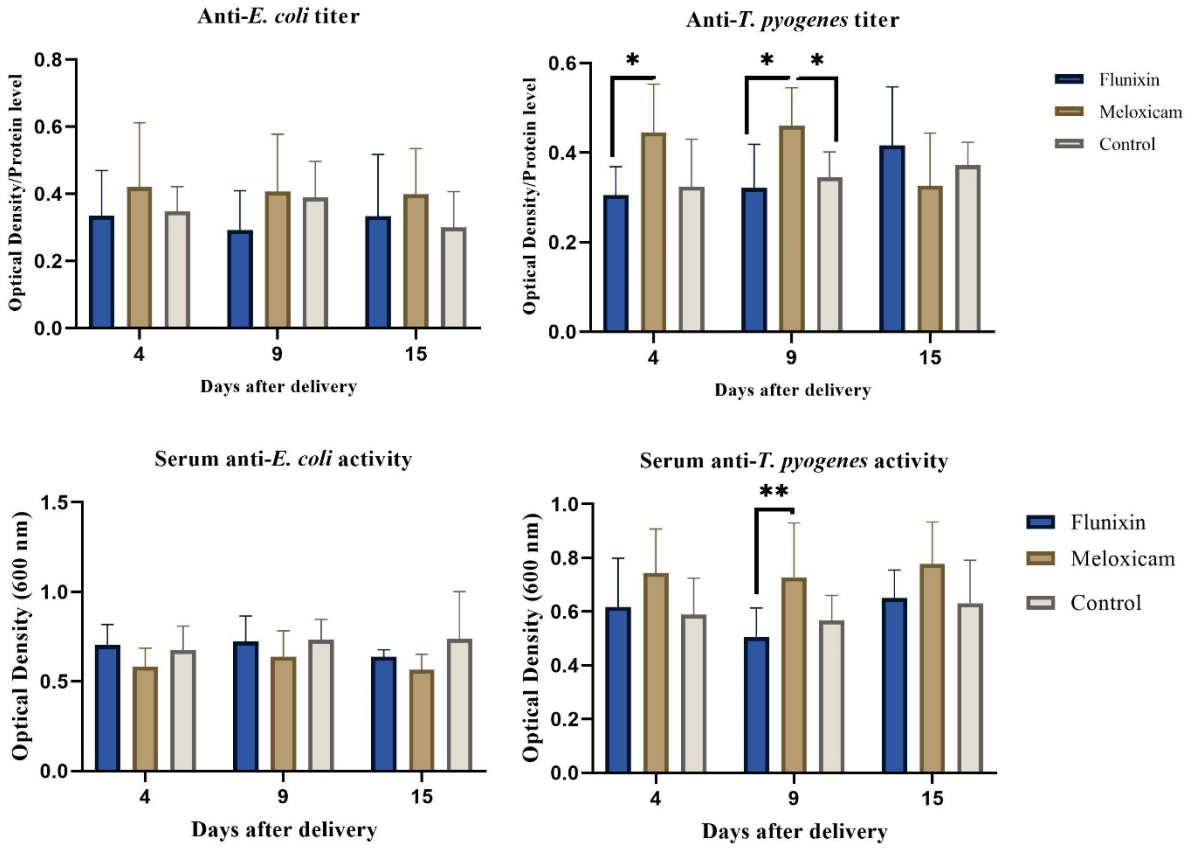

Figure 2. The cattle serum immunoglobulin (Mean±SD) titer (A and B) and antibacterial activity (C and D) against *E. coli* and *T. pyogenes* in cows treated by flunixin, meloxicam and control groups

Note: The single asterisk (*) denotes a significance level of P<0.033, two asterisks (**) indicate a significance level of P<0.002, and three asterisks (***) represent a significance level of P<0.001.

current study demonstrated an increase in antibody titer and antibacterial activity against *T. pyogenes*, however, no significant difference in antibody titer or antibacterial activity against *E. coli* were observed compared with the control group. This indicates that NSAIDs treatment did adversely affect the main humoral components of the innate and adaptive immune responses. However, the results revealed certain points and limitation that will be discussed in the following sections.

The presence of IgA-secreting cells in the vagina and the secretion of blood or endometrial IgG into the uterus constitute the primary humoral immunity of the reproductive system in cattle. These antibodies can directly neutralize uterine infectious agents or indirectly enhance the phagocytosis through opsonizing them or stimulating complement pathways [16]. Evidence suggests a correlation between systemic or local immunization and its effect on the levels of specific antibody titers in the uterus or bloodstream [17]. The induction of local specific antibody titers, including IgM, IgG, and IgA, following local challenges with *C. fetus* has previously been reported by Corbeil et al. (1974) [18]. However, antibody isotype may be influenced by the type of stimulating antigens [19]. Therefore, in line with the results of the mucosal antibacterial and antibody titer against *T. pyogenes* in the current study, it is not surprising to observe the effects of systemic modifications of immune responses on the regulation of the mucosal immunity.

In agreement with the higher non-significant titer against *E. coli* and significant elevation of antibody titer against *T. pyogenes* in the meloxicam- treated group, previous research revealed that weaned calves treated with meloxicam exhibited elevated antibody titers following vaccination against bovine respiratory syncytial virus, bovine herpesvirus type 1, parainfluenza virus type 3, and coronavirus, as well as increased serum bactericidal activity. However, these treated animals showed a higher risk of treatment-related complications [19]. Duffield et al. (2009) administered flunixin at a dose of 1.25 g intramuscularly (I.M.) for cows and 1.1 g for heifers. Treatment was given approximately 2 hours after calving, with a second dose administered approximately 24 hours later. No significant effects of treatment were observed on the risk of subsequent hypocalcemia, displaced abomasum, clinical ketosis, mastitis, or milk yield. However, cows treated with flunixin were more likely to retain their fetal membranes and had an increased risk of developing metritis [20].

The highest concentrations of total secretory immunoglobulin A (sIgA) antibodies were found in the vaginal mucus of cows treated oronasally with LPS. This indicates that oronasal LPS can induce a short-lived IgA response in the vagina of dairy cows. Inducing an immune response in the genital tract of transition cows is crucial, as uterine infections are prevalent and can lead to infertility, making them the primary reason for the culling of dairy cows [21]. Previously, dose-dependent effects of flunixin and meloxicam on leukocytes in calves have been reported [22]. Furthermore, Bednarek et al. (2003) documented the immunosuppressive benefits of both medications in calves affected by enzootic bronchopneumonia. They also proposed a combined therapy using antibiotics and meloxicam for calves, which resulted in increased interferon-gamma levels, although no changes in immunoglobulin concentration were detected four days post-treatment [23]. Pascottini et al. (2020) reported that administering meloxicam once daily for four days, starting two weeks postpartum, reduced systemic inflammatory responses but did not affect the inflammatory status of the endometrium [8]. In the present study, treatment was administered three days after delivery, allowing initial inflammatory immune responses to occur within the first three days post-delivery. This early inflammatory phase may play a beneficial role in host defenses against infectious microorganisms and in tissue repair following parturition. Therefore, the insignificant effects observed in the bactericidal tests and antibody titers support the hypothesis of the current study.

Oral administration of meloxicam in beef cattle treated with LPS did not influence neutralizing antibody titer following vaccination against respiratory pathogens, nor did it affect the acute-phase proteins or of TNF-α levels [24]. Similarly, the current study found no significant difference in uterine antibody titer against *E. coli*. Similarly, previous research exhibited that transdermal flunixin meglumine had no effects on antibody titers against *Mannheimia haemolytica* in beef heifers [25].

5. Conclusion

The current study evaluated the effects of systemic injections of flunixin and meloxicam on local uterine immunity against two primary pathogenic bacteria. The results indicated no significant difference in specific antibody levels or antibacterial activity against *E. coli* among the flunixin, meloxicam, and control groups at the same time point. This finding contrasts with some studies suggesting that NSAID administration is associated with immunosuppression effects. Also, the anti-*T. pyogenes* antibody titer was higher in meloxicam-

treated animals at day four days after calving (one day post-treatment) compared with the flunixin group. In the meloxicam- treated group, local vaginal antibody titers may be neutralized due to increased exposure to *T. pyogenes*, resulting in decreased antibody titers on day 15. Furthermore, unlike the steady-state antibody titers observed in the meloxicam group on days 4 and 9, the induction of a humoral immune response against *T. pyogenes* during the 15 days following calving led to a non-significant elevation in antibody titers in the control and flunixin groups. These results suggest that, in addition to the humoral factors evaluated in the current study, the role of innate immune cells should also be assessed better elucidate the effects of meloxicam. Overall, the data indicate no adverse effects of treatment with flunixin and meloxicam on humoral elements of uterus mucosal immunity. However, differing effects of NSAIDs treatment were observed on antibody titers and antibacterial activity against *E. coli* and *T. pyogenes* pathogens. The observed differences can be ascribed to pathogen-specific immune responses directed towards specific pathogens, as well as fluctuations in bacterial density within the environment. It is essential for veterinarians to take into account farm management strategies when prescribing flunixin and meloxicam in postpartum dairy cows.

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Compliance with ethical guidelines

All animal experiments were carried out in accordance with animal protection laws and guidelines of Research Ethics Committee of Shahid Chamran University of Ahvaz, Ahvaz, Iran (Code: IR.SCU.REC.1403.022).

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Authors' contributions

Conceptualization, study design, project administration, technical, and material support: Mohammad Khosravi and Saad Gooraninejad; Investigation, data acquisition, experiments, data interpretation, and writing the original draft: Mohammad Khosravi and Ali Rahmati; Review and editing: Mohammad Khosravi; Statistical analysis: Mohammad Khosravi and Meaysam Makki; Supervision: Mohammad Khosravi, Saad Gooraninejad, Meaysam Makki and Mohammad Nouri; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

Data availability

All analyzed/raw data are available from the corresponding author upon request.

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