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Effects of non-steroidal anti-inflammatory drug administration following parturition on milk yield, postpartum disorders and reproductive parameters in lactating dairy cows

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ABSTRACT

In this study, effects of carprofen, as a long-acting non-steroidal anti-inflammatory drug (NSAID), administration to decrease pain following calving on changes in body weight (kg) between days 1-15, 15-30 and 1-30 postpartum, the first 150 days milk yield, postpartum diseases, milk electric conductivity scores, estrous activities based on pedometer and reproductive parameters were investigated in lactating cows. Physiologic saline (Control; n=50) or Carprofen (1.4 mg/kg; Rimadyl®, n=50) was administered subcutaneously within 12 hours following parturition. All cows were normally calved (eutocia). Vaginal discharge was visually examined on 25-32 days postpartum. Cows were artificially inseminated (AI) following Ovsynch protocol or estrus detected with pedometer. Incidences of retained foetal membranes, metritis, mastitis were not differed between groups. Occurrence of pathological vaginal discharge was significantly ($P<0.05$) higher in Carprofen (25.6% [10/39]) group than that in Control (7.3% [3/41]) group. There were no differences in intervals from calving to the first detected estrus and AI, pregnancy per AI, changes in body weight nor 150 days milk yield between groups. Rate of at least one detected estrus until 70 days postpartum was significantly ($P<0.05$) higher in Control (97.7% [42/43]) group than that in Carprofen (84.6% [33/39]) group. In conclusion, Carprofen administration following calving did not increase milk yield or fertility in eutotic Holstein cows in this study. Furthermore, no increase in the incidence of retained foetal membranes or metritis following carprofen administration in this study could allow to use of carprofen immediately after calving for therapeutic purposes in eutotic cows.

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Introduction

Parturition is a crucial moment for the health and welfare of the cow (Laven et al., 2012). The welfare of an animal is defined as its state with regard to its efforts to deal with its environment (Broom, 1986). In this matter, inflammation and pain are anticipated to be more prevalent and critical in primiparous cows due to narrower pelvic region, slower parturition and deficient vulva dilatation (Mee, 2004). Pain care following parturition could be useful for a cow by causing a better appetite leading to more milk production (Stilwell et al., 2014). Although non-steroidal anti-inflammatory drugs (NSAIDs) contain analgesic, anti-inflammatory, anti-endotoxic and anti-pyretic impacts in cattle, NSAID's are less likely to be used pain management following calving (Laven et al., 2012). Pregnancies in cattle may be subject to dystocia

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ectopic at a rate of 3-25%, which causes a significant economic loss in breeding. Nutrition and environmental factors are among the causes of dystocia. Body condition score, oxidative stress, mineral substance balance in the diet and dry period nutrition, housing conditions, climate and geographical location are factors that predispose to dystocia. The incidence of dystocia can be reduced with a balanced diet, appropriate reproductive management and good livestock practices (Günay Uçmak and Kurban, 2023).

NSAIDs have light organic acid constitution with a broad range of structures suppress cyclooxygenase (COX) enzyme in the arachidonic acid cascade leading to lessen the release of prostaglandins (Espinasse et al., 1994; Vane, 1971). Xie et al. (1991) reported that COX enzymes are in two isoforms including COX1, plainly fundamental, and COX2, an inducible. Because COX2 enzyme primarily leads to production of prostaglandins associated with inflammation, fever and pain, therapeutic impacts of NSAIDs, including peripheral and central analgesia, anti-inflammatory, anti-pyretic and anti-endotoxic effects are attributed to suppression of COX2 enzyme (Fitzpatrick et al., 2004). Among NSAIDs, carprofen non-selectively supresses COX-1 and COX-2 enzymes in cattle (Brentnall et al., 2012). That is why carprofen was reported as a treatment of choice, as an analgesic, for painful cases in cattle (Stilwell et al., 2008).

Antanaitis et al. (2018) reported decrease in concentration of blood cortisol reflecting stress for 48 hours following parturition in primiparous dairy cows administered carprofen within one hour after from calving. Moreover, higher pregnancy rate, shorter calving interval, lower somatic cell count in milk and lower incidences of retained fetal membranes (RFM), metritis and clinical mastitis have been reported in primiparous dairy cows administered carprofen within one hour after from calving (Antanaitis et al., 2018). Stilwell et al. (2014) observed 2.593 L more milk in primiparous but not in multiparous dairy cows administered carprofen (1.4 mg/kg) within six hours after from calving. Stilwell et al. (2014) attributed this beneficial effect of carprofen administration on milk yield to its analgesic effect resulting in sooner feed consumption following parturition in primiparous cows.

Higher reproductive performance based on pregnancy rates were reported in response to NSAID administration following calving (Antanaitis et al., 2018; Giammarco et al., 2018; Stilwell et al., 2014). In literature, there was no study to investigate effect of NSAID administration following calving on estrous expression rate and subclinical mastitis based on milk electrical conductivity during postpartum period. Therefore, it was aimed to investigate effect of carprofen administration following calving on milk yield, reproductive performance and incidences of postpartum diseases/disorders along with mastitis in lactating cows in this study.

Materials and Methods

Animals and experimental design

This study was approved by Local Ethical Committee for Animal Experiments at Balıkesir University (File Number: 2020/4-11, 25.06.2020). This study was conducted in commercial dairy farm located in Balıkesir, Türkiye. Holstein dairy cows were milked freely for 24 hours in Robotic milking system. Lactating Holstein cows were fed (26 kg dry matter/head/day) with total mixed ration (%3.6 wheat hay, %12 alfalfa, % 51.6 corn silage, %3 soy bean meal, %9 corn flake, %3.6 crushed barley grain, %9.6 sugar beet pulp, %0.6 molas, %4.8 concentrated feed, %0.96 by-pass fat, %0.96 buffer, %0.3 yeast) including 2900 kcal metabolic energy and %14.6 crude protein. Primiparous (n=27) and multiparous (n=73) cows with single offspring were randomly divided into two groups, and then physiologic saline (Control; n=50) or Carprofen (1.4 mg/ kg; Rimadyl®, Zoetis Animal Health, Türkiye; n=50) were administered subcutaneously within 12 hours following calving.

Clinical examinations and records

Calving scores in 1-4 scale (1: normal; 2: slight calving difficulty, assistance with one person without use of mechanical equipment; 3: severe dystocia, assistance with more than one person or use of mechanical equipment; 4. severe dystocia resulted in C-section) were recorded as reported by Meyer et. al., (2001).

Cows were visually examined for vaginal discharges at 25-32 days postpartum, and vaginal discharges were classified in 0-3 scale (0: bright or transparent; 1: discharge containing particles of white or off-white purulent content; 2, including ≤50% white or off-white mucopurulent content; and 3, including ≥50% purulent content, generally white or yellow, but rarely bloody discharge) as reported by (Williams et al., (2005). In order to perform discrete analyses, vaginal discharge scores below two were accepted as normal, and vaginal discharge scores equal to or above two were accepted as pathologic.

Cows did not expel the placenta 48 hours after from calving was accepted as RFM case. Cows having malodorous, purulent or bloody vaginal discharge, along with at least one systemic symptoms including fever, anorexia, fatigue were accepted as a metritis case. Presence of oedema, redness, sensibility, swelling, colour changes, fleck of pus, odor and positive results of CMT test in milk in at least one mammary gland was accepted as clinical mastitis. Subclinical

mastitis cases were determined based on milk electrical conductivity by milking system for the first 150 days during lactation.

Data for total milk yield (kg) for 150 days, live body weight (kg) on the day 0 (calving), 15 and 30 postpartum, clinical and subclinical mastitis cases, postpartum health records, estrous records based on pedometer system, the first service pregnancy rates was obtained from computerized herd management system (Lely™, Lely T4C-Time for cows, Netherlands).

In this study, routine postpartum reproductive protocol of farm was followed. In this matter, cows were mainly inseminated following Ovsynch protocol, or detection of estrus based on pedometer. In all artificial inseminations (AI), conventional sperma with proven fertility were used. Pregnancies were diagnosed with transrectal ultrasonography 30-35 and 60-70 days after from AI.

Statistical Analysis

All statistical analysis were performed with MedCalc (MedCalc® Statistical Software version 20.007 [MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021]) program. Differences for milk yield, body weight, period time lengths from calving to the first estrous and from calving to the first AI between two experimental groups were analysed with two way ANOVA test. Mathematical model for all two way ANOVA analysis includes treatment, parity and interaction of treatment, by parity. Results were expressed as mean and standard error of mean.

All categorical analysis including rates of dystocia, RFM, pathological vaginal discharge, metritis, clinical and subclinical mastitis, estrous detection, the first service pregnancy between two experimental groups were analysed with Chi-squared test.

Results

There was no dystocia, and all cows calved normally (calving score: 1). There were no differences for the incidence of RFM, metritis, clinical mastitis and subclinical mastitis between experimental groups (Table 1). Rate of pathological vaginal discharge on days 25-32 postpartum was statistically higher (P<0.05) in Carprofen treated group (%25.6 [10/39]) compared to that in Control group (%7.3 [3/41], Table 1).

There were no differences for days in milk at the first detected estrus based on pedometer and the first AI between experimental groups (Table 2). However, rate of detected estrus until 70 days postpartum was significantly (P<0.05) higher in Control group (%97.7 [42/43]) compared to that in Carprofen treated group (%84.6 [33/39]) (Table 2). Whereas, P/AI following the first AI postpartum did not differ between experimental groups (Table 2).

Table 1. Distribution of postpartum diseases and disorders between experimental groups.

Disease/Disorder	Control	Carprofen
Dystocia (%; n/n)	% 0 (0/50) [a]	% 0 (0/50) [a]
Retained fetal membranes (%; n/n)	% 6 (3/50) [a]	% 10 (5/50) [a]
Pathological vaginal discharge (%; n/n)	% 7.3 (3/41) [a]	% 25.6 (10/39) [b]
Metritis (%; n/n)	% 2 (1/50) [a]	% 4 (2/50) [a]
Clinical mastitis (%; n/n)	% 0 (0/50) [a]	% 2 (1/50) [a]
Subclinical mastitis (%; n/n)	% 26.1 (12/46) [a]	% 43.2 (19/44) [a]

a,b Different superscripts within row indicates statistical significance (P<0.05).

Table 2. Days in milk (mean and standard error of mean) at the first detected estrus and the first AI along with rate of the detected estrus and pregnancy per AI after the first service

Reproductive parameters	Control	Carprofen
Days in milk at the first detected estrus until 70 days post-partum.	37.95 ± 2.58 [a] (n=42)	35.22 ± 3.95 [a] (n=33)
Rate of detected estrus until 70 days postpartum (%; n/n).	%97.7 (42/43) [a]	%84.6 (33/39) [b]
Days in milk at the first AI	84.07 ± 3.69 [a] (n=49)	81.82 ± 4.84 [a] (n=46)
Pregnancy per AI after the first service (%; n/n)	%20.5 (9/44) [a]	%15.4 (6/39) [a]

a,b Different superscripts within row indicates statistical significance (P<0.05).

Table 3. Differences and changes in body weight (kg; mean and standard error of mean) between experimental groups.

Time of body weight (kg) measurement	Control (n= 37)	Carprofen (n= 42)
On the day (0) of calving	648.95 ± 11.69 [a]	646.56 ± 15.86 [a]
15 days after from calving	615.63 ± 11.49 [a]	609.38 ± 15.59 [a]
30 days after from calving	600.65 ± 11.66 [a]	596.26 ± 15.81 [a]
Between 0-15 days after from calving	-33.32 ± 5.20 [a]	-37.18 ± 7.06 [a]
Between 15-30 days after from calving	-14.98 ± 4.41 [a]	-13.12 ± 5.98 [a]
Between 1-30 days after from calving	-48.30 ± 7.23 [a]	-50.30 ± 9.81 [a]

a,b Different superscripts within row indicates statistical significance (P<0.05).

Table 4. Distribution of 150 days milk yield (kg; mean and standard error of mean) among treatment groups and parity.

Parity	**Control (n=44)**	**Carprofen (n=39)**
Primiparous (n=21)	5256.38 ± 281.35 [a] (n=16)	4926.28 ± 503.29 [a] (n=5)
Multiparous (n=62)	6517.45 ± 212.68 [a] (n=28)	6166.59 ± 193.00 [a] (n=34)
All cows (n=83)	5886.91 ± 176.34 [a]	5546.43 ± 269.51 [a]

a, b Different superscripts within row indicates statistical significance (P<0.05).

No differences were detected for body weight of cows on days 1, 15 and 30 following calving between experimental groups (Table 3). Similarly, there were no differences in body weight changes during the first fifteen days, the second fifteen days or the first 30 days following parturition between experimental groups (Table 3).

There was no difference for 150 days milk yield between experimental groups (Table 4). Likewise, there was no interaction effect of treatment by parity for 150 days milk yield, and similar trends were observed for 150 days milk yield between experimental groups in both primiparous and multiparous cows (Table 4).

Discussion

It has been known that uterine muscles do not contract in response to excessive amounts of PGF2α secretion from uterine and non-uterine sources due to uterine infections, and uterine involution is delayed (Kindahl et al., 1992). Tended to be lower incidence of RFM following ketoprofen administrations immediately after from parturition and 24 hours later in Holstein dairy cows was reported (Richards et al., 2009). In this matter, Richards et al. (2009) postulated that ketoprofen with anti-inflammatory and anti-endotoxic effects decrease inflammatory response could cause normal involution leading to faster expulsion of fetal membranes. Newby et al. (2014) reported that meloxicam administration within one hour following calving did not increase the incidence of RFM and periparturient diseases in Holstein dairy cows. No differences for the incidence of RFM were reported meloxicam administration prior to or after parturition compared to control group in cows (Swartz et al., 2018). Similarly, Stilwell et al. (2014) reported no difference for the time of the expulsion of the fetal membranes and incidence of clinical diseases during three days postpartum following carprofen administration with in six hours after parturition compared to control cows in Holstein dairy cows. Moreover, Antanaitis et al. (2018) reported lower incidence of RFM in response to carprofen administration within one hour following calving in first -lactation cows. Furthermore, no differences were reported for incidence of RFM in cows administered carprofen or flunixin meglumine within 12 hours after calving compared to control group; however, lower incidence of RFM was reported in multiparous cows administered flunixin meglumine (Giammarco et al., 2018). In contrast, Newby et al. (2017) reported that administration of flunixin meglumine within one hour after calving increased the risk of RFM in cows. Swartz et al. (2018) postulated that different results from different NSAID administrations could be due to

different effects of different NSAID's administered at different times following calving. In this regard, Newby et al. (2017) and Swartz et al. (2018) concluded that higher risk of RFM following flunixin meglumine administration in cows could be owing to stronger suppression of COX-1 enzyme in response to flunixin meglumine administration as reported by Beretta et al. (2005). Likewise, no detrimental effect of carprofen administration following calving on the incidence of RFM in current study is in agreement with previous studies.

Similar to Giammarco et al. (2016) no effects of carprofen administration following calving on the incidences of metritis, clinical and subclinical mastitis were observed in current study. Likewise, no effect of administration of meloxicam prior to or following calving on the incidences of metritis and clinical mastitis (Swartz et al., 2018). Similarly, Richards et al. (2009) reported no effect of ketoprofen administrations immediately after from parturition and 24 hours later on endometritis score in Holstein dairy cows. Contraversely, Antanaitis et al. (2018) reported lower incidences of metritis and clinical mastitis and lower somatic cell count in milk with regards to carprofen administration following calving. No effect of carprofen administration on incidences of metritis, clinical and subclinical mastitis could be attributed to no dystocia cases and robotic milking system with better milking hygiene in present study.

In spite of increase in the rate of pathological vaginal discharge, carprofen administration following calving did not increase incidence of metritis in this study. In this matter, higher incidence of pathological vaginal discharge could be attributed to suppression of PGF2α from endometrium, in response to NSAID administration following calving, leading to impaired involution in present study. In this matter, Thun et al., (1989) reported that a single dose of carprofen (0.7 mg/kg) administration effectively suppressed PGF2α release in the postpartum cow. However, it has been thought that normal release of PGF2α after completion of half-life of carprofen, for almost three days, could stimulate uterine involution; thereby, it could prevent the presence of metritis in current study. Similar to this assumption, it has been reported that administration of carprofen either on days 1, 3, 5 or 19, 21, 23 following calving did not have any effect on vaginal mucus score based on Metri-check device and proportion of polymorph-nucleated cells following cytobrush technique on 13-24 and 30-49 days postpartum (Meier et al., 2014).

No differences for the time intervals from calving to the first detected estrus and from calving to the first AI could indicate the absence of any detrimental effect of carprofen administration following calving on fertility in current study. Likewise, Giammarco et al. (2016) reported no differences for the time intervals from calving to the first detected estrus and from calving to the first AI in response to carprofen or flunixin meglumine administrations within 12 hours following calving compared to those in untreated cows. Similarly, no effects of ketoprofen administrations immediately after from parturition and 24 hours later on incidence of corpus luteum detected with transrectal ultrasonography at a pre-breeding examination on days 20 to 25 postpartum and interval from calving to the first AI in Holstein dairy cows were reported (Richards et al., 2009). Furthermore, Priest et al. (2013) reported no differences for the time of the first ovulation (based on plasma progesterone ≥1 ng/mL) during postpartum period in grazing dairy cows with three subsequent carprofen administrations once in three days between days 21 – 31 following calving. Lower rate of detected estrus until day 70 postpartum in carprofen treated group could indicate the negative effect of the delay of the uterine involution in current study. However, no relationship between rates of pathological vaginal discharge and estrous detection could reveal any other mechanism to suppress estrous expression in response to carprofen administration following calving in current study.

While, there was no effect of carprofen administration following calving on the first service pregnancy rate in this study, Giammarco et al. (2016) reported higher pregnancy rates at the first service in cows administered either carprofen or flunixin meglumine within twelve hours following calving. Similarly, Antanaitis et al. (2018) indicated 8.5% increase in pregnancy rate in primiparous Holstein cows administered carprofen within one hour following calving. In contrast, Stilwell et al. (2014) reported lower pregnancy rate in cows administered carprofen within six hours following calving, and they assumpted that higher milk production following carprofen administration could result in delay of resumption of ovarian cyclicity leading to lower pregnancy rate. These discrepancies for fertility among these studies could be due to differences in sample sizes, parity distributions and reproductive management systems. That is why more controlled studies with adequate sample sizes under standard reproductive management to investigate effect of NSAID administration on fertility following calving are required. Numerically lower pregnancy rate in carprofen treated group could be attributed to lower ovarian cyclicity rate based on estrous detection during postpartum period in

carprofen treated group in this study. In this matter, lower rate of detected estrus until day 70 postpartum in carprofen treated group could indicate the negative effect of delayed involution on ovarian cyclicity; however, this significantly lower estrous detection rate until day 70 postpartum did not reflect on pregnancy rates in carprofen treated group in this study. Since most of the cows were inseminated at fixed time insemination (FTAI) following synchronization of ovulation (Ovsynch) protocol, acyclic cows could recover following GnRH injections until FTAI in this study.

No changes for body weight during monitored period could indicate no increase in feed consumption following a single carprofen administration with its analgesic and antipyretic effects post calving in this study. Similarly, Giammarco et al. (2016) reported no effect of carprofen administration within 12 hours after calving on body weight during postpartum period. No beneficial effect of carprofen administration following calving on body weight changes could be due to absence of dystocia cases in present study, and more controlled studies including both eutotic and dystosic cows would be required for better comparison.

Effect of NSAID administration on milk yield was more effectively observed during peak of lactation in dairy cows (Carpenter et al., 2016; Trevisi & Bertoni, 2008). Since 150 days total milk yield obtained from automated daily milk records was provided in current study, it has been thought that the effect of NSAID administration on milk yield could be strictly revealed. Similar to no main effect of treatment nor interaction effect of treatment by parity on 150 days total milk yield following carprofen administration in this study, Giammarco et al. (2016) reported no main effect of treatment nor interaction effect of treatment by parity on 60 days total milk yield following carprofen or flunixin meglumine administration within 12 hours after calving. Likewise, Meier et al. (2014) reported no effect of carprofen administration on days 1, 3, 5 or 19, 21, 23 following calving on six weeks total milk yield. Similarly, no effect of ketoprofen administrations immediately after from parturition and 24 hours later on milk production at the first recording was reported (Richards et al., 2009). In contrast, Antanaitis et al. (2018) noted 252 kg more milk for 305 days milk yield in primiparous Holstein cows following carprofen administration within one hour after calving. Stilwell et al. (2014) reported an increase in 305 days milk yield in response to carprofen administration within six hours following calving in primiparous but not in multiparous cows. Swartz et al. (2018) indicated a tendency ($P<0.07$) for increase in milk yield following meloxicam administration after parturition in eutotic but not in dystosic cows. Swartz et al. (2018) speculated that increase in milk yield following NSAID administration could be due to proliferation of mammary epithelial cells or decrease in involution along with apoptosis in mammary gland. In this regard, Bertoni et al. (2008) reported that cows with higher degree of inflammation produced 20% lower milk compared to those with lower degree of inflammation. No difference for milk yield following carprofen administration could be attributed to higher proportion of multiparous cows and no dystocia cases in current study. Better animal welfare could overlap any beneficial effect of NSAID administration following calving on milk yield since cows voluntarily were milked for 24 hours in robotic milking system in this current study.

Conclusion

In conclusion, NSAID administration following calving as a farm routine did not increase milk yield or fertility in eutotic Holstein cows in this study. However, no increase in the incidence of RFM or metritis in response to NSAID administration following calving in eutotic cows could indicate that carprofen could be used immediately after calving upon needed for therapeutic purposes. Because no dystocia cases were observed in this study, further research is warranted to investigate any beneficial effect of NSAID administration following calving on milk yield and fertility in eutotic versus dystosic cows with different parities.

Conflicts of Interest: The authors declare no conflict of interest.

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