Effects of meloxicam on milk production, behavior, and feed intake in dairy cows following assisted calving

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ABSTRACT

Parturition is a necessary event for production in dairy cattle, and assistance at calving is common. There is limited use of nonsteroidal antiinflammatory drugs for the alleviation of calving pain and a paucity of research on the effects of these drugs on postpartum health and performance. This randomized triple blind clinical trial involved Holstein cows ($n = 42$) and heifers ($n = 61$) that experienced an assisted parturition. These animals received either 1 injection of meloxicam (0.5 mg/kg of body weight) or placebo subcutaneously 24 h following calving. Outcome measures included dry matter intake (DMI) and milk production for the first 14 d in milk, blood metabolites sampled over 12 d, health events for the first 60 d in milk, as well as lying and feeding behavior 24 h following injection. Continuous data were analyzed using multivariable regression models. Binary outcomes were analyzed using a mixed logistic model with cow modeled using a random intercept. This study failed to show any significant effects of treatment on DMI, milk production, blood metabolites, or health events. A possible explanation for the lack of treatment differences could be that the meloxicam was administered too late after calving. Meloxicam increased feeding time as well as bunk visit frequency in the 24 h following injection. Regardless of treatment, animals that had retained fetal membranes produced less milk and had higher serum haptoglobin concentrations. Future research is warranted to examine the effects of antiinflammatory drugs administered closer to the time of calving on health and production.

Key words: nonsteroidal antiinflammatory drug, dystocia, pain, welfare

INTRODUCTION

Parturition is necessary for dairy production and assisted calving is common. Calving is a painful event that leads to inflammation (Bionaz et al., 2007). Dystocia rates are higher in North America ($>10\%$) compared with other parts of the world ($<5\%$), and, regardless of country, are much higher in primiparous animals (Mee, 2008). Severe dystocia (i.e., cases requiring either heavy tractive force with a calf puller, extensive corrections of malpositions, or caesarean section) was associated with reduced viability of the calf and reduced fertility and survival of the dam (Tenhagen et al., 2007). Dystocia negatively affected early lactation performance in Holstein cows, with peak yield lowered by 0.39, 2.2, 2.2, and 2.5 kg for cows in parities 1 to 4, respectively (Atashi et al., 2012). Dystocia is a risk factor for metritis and for purulent vaginal discharge (Dubuc et al., 2010).

In a questionnaire to cattle veterinarians in the United Kingdom, the median estimate of pain of dystocia was 7 out of 10 (Huxley and Whay, 2006). Sixty-six percent of respondents indicated using a nonsteroidal antiinflammatory drug (NSAID) in some cases of dystocia (Huxley and Whay, 2006). In a survey on analgesic use among Canadian veterinarians in 2004–2005, the mean estimate of pain level was 5.3 out of 10 (Hewson et al., 2007). Thirty-four percent of veterinarians provided analgesia to some or all cases of dystocia (Hewson et al., 2007). Despite the apparent recognition that dystocia is painful, little is known about the effects of pain resulting from difficulty or assistance at calving on production or health, or about the effects of NSAID to treat dystocia (Laven et al., 2012) and thus more work is warranted. In addition, there is a paucity of data on approaches to control this pain with medication. Insofar as we know, this is the first study to evaluate the short-term benefits of NSAID treatment following dystocia, despite the relatively common use of NSAID by veterinarians (Laven et al., 2012).

Consumption of amniotic fluid by the cow was shown to provide some analgesic effect from endogenous opioids (Pinheiro Machado et al., 1997). Current recom-

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mended management practices, such as removing the calf immediately after birth (National Farm Animal Care Council, 2009), and the relatively high incidence of dystocia likely result in many cows not being able to benefit from the ingestion of amniotic fluid. Therefore, some analgesic assistance in the form of an antiinflammatory drug may prove to be beneficial to these animals. The objective of this study was to evaluate the effect of meloxicam on behavior, health, and production in cows with assisted calving. The hypothesis was that the administration of meloxicam following assisted calving would improve feed intake and milk production and reduce inflammation and pain in dairy cows.

MATERIALS AND METHODS

General Information

This randomized controlled trial involved Holstein cows ($n = 42$) and heifers ($n = 61$) that experienced assisted parturition at the Elora and Ponsonby Dairy Research Centers, University of Guelph (Guelph, ON, Canada), with enrollment into the study taking place between January 2009 and January 2011. Calving difficulty was scored as follows: 1, an easy pull by one person with no mechanical assistance, or 2, a difficult pull with more than one person, with mechanical assistance, or a combination of both. Cows that had a fetotomy or caesarean section were excluded. Whether the animal had retained fetal membranes at 24 h postcalving was recorded systematically. Animals with assisted calving were blocked into primiparous and multiparous groups, and into calving difficulty, and randomly assigned within blocks to receive meloxicam [$n = 51$; 0.50 mg/kg of BW, Metacam 20 mg/mL solution for injection; Boehringer Ingelheim (Canada) Ltd., Burlington, ON, Canada] subcutaneously once 25.4 h (± 2.9 SD) following calving or to be negative controls ($n = 52$; injection of a similar volume of placebo (the medication vehicle solution with no active ingredient once 25.0 h ± 2.8 SD). Personnel administering the treatments, recording data, and performing statistical analyses were blinded to treatment assignments.

Cows were housed in tie-stalls through the previous lactation and late gestation, and heifers were loose housed until 9 wk before expected calving when they were moved to a tie-stall. All animals were moved to individual calving pens (7.0 $\times$ 3.1 m; straw pack bedding in one half and wood shavings over mattress filled with rubber crumbs in the other half) 2 d (± 1.8 SD) before expected calving based on their due date and appearance of early calving signs (e.g., filling of the udder). Cows remained in the maternity pen for 2 d (± 0.69 SD) after parturition before moving to the tie-stall for lacta-

tion. All animals in both barns were fed the same TMR twice daily (0730 and 1300 h) for ad libitum intake. The diet in the calving pens was composed of 1 kg of hay, 1.6 kg of haylage, 6.6 kg of corn silage, 0.80 kg of high-moisture corn, and 2 kg of commercial protein and mineral supplement for dry cows (DM basis: CP: 14% DM, ADF: 23–25% DM, NDF: 35–40% DM, fat: 3.6–3.8% DM, and net energy: 1.45 Mcal/kg). The lactation diet was composed of 1.5 kg of hay, 6.2 kg of haylage, 6.2 kg of corn silage, 4.8 kg of high-moisture corn, and 5 kg of supplement containing soybeans, vitamin, protein, and mineral (DM basis: CP: 17% DM, ADF: 20–21% DM, NDF: 30–35% DM, fat: 3.6–3.8% DM, and NE: 1.62–1.67 Mcal/kg) and formulated to meet requirements (NRC, 2001) for a 650-kg cow producing 35 kg/d of milk at 3.8% fat. Tie-stalls had feed dividers between cows so that individual feed intakes could be measured.

DMI, Milk, and BW Data

Individual daily feed intakes were recorded from the time the cow entered the maternity pen and then in the tie-stalls until 14 DIM. Samples of the prepartum diet and the early-lactation diet were collected twice weekly and frozen at -20°C for later analysis. Intake calculations were based on the amount fed to the animal, theorts recovered, and the DMI analysis of the samples. Milk yield was recorded twice daily until 14 DIM. All cows were weighed at enrollment in the study (2 d before expected calving at movement into the calving pen) and at 60 DIM.

Blood Collection and Analysis

Blood samples were obtained by coccygeal venipuncture immediately after calving and 1, 3, 6, 9, and 12 DIM. The d 1 blood sample was taken at the time of treatment administration and all other blood samples were taken in the morning, approximately 3 h after feeding, allowed to clot for 1 h, and centrifuged at $7,000 \times g$ (model CL international clinical centrifuge, International Equipment Co., Needham, MA) to collect the serum. Blood serum was frozen and submitted for analysis to the Animal Health Laboratory, University of Guelph. Serum was analyzed for BHBA, NEFA, glucose, calcium, and haptoglobin. All analyses were conducted using a Roche Cobas 6000 c501 automated chemistry analyzer (Roche Canada, Laval, QC, Canada). The NEFA and BHBA concentrations were determined using Randox NEFA and Randox BHBA kits (Randox Laboratories Canada Ltd., Mississauga, ON, Canada); the analytical sensitivity was 0.10 mmol/L for both assays. The inter- and intraassay coefficients of variation

were 1.0 and 6.3%, respectively, for NEFA, and 0.50 and 1.6%, respectively, for BHBA. Glucose concentrations were measured using the Roche GLUC3 kit (Roche Diagnostics, Laval, QC, Canada). The analytical sensitivity of the glucose assay was 0.10 mmol/L, and the inter- and intra-assay coefficients of variation were 2.9 and 2.4% respectively. Calcium concentrations were measured with a commercial kit (Roche Diagnostics). The analytical sensitivity of the calcium assay was 0.10 to 5.0 mmol/L, and inter- and intraassay coefficients of variation were 2.1 and 3.3%, respectively. Haptoglobin concentrations were measured by determining the hemoglobin binding capacity, using a methemoglobin reagent made on site (see Skinner et al., 1991; Skinner and Roberts, 1994). The analytical sensitivity of the haptoglobin assay was 0.03 g/L; inter- and intraassay coefficients of variation were 5.9 and 5.3%, respectively.

Health Events

Rectal temperatures for the first 10 d postcalving were taken in the morning using a digital rectal thermometer (Digital Fever Thermometer, Omron Healthcare Inc., Vernon Hills, IL). All clinical health events and treatments were recorded for each cow enrolled in the study up to 60 d postcalving. Diseases of interest for their possible confounding effect included the occurrence of retained fetal membranes, milk fever, clinical mastitis, clinical ketosis [clinical signs include anorexia, depression, and positive ketone test in the milk (BHBA ≥ 100 μ mol/L)] or urine ketone test ("small" or greater on Ketostix strips; Geishauser et al., 1998), metritis (systemic illness including fever $>39.5^{\circ}\text{C}$ with fetid discharge from the vulva; LeBlanc et al., 2002), and displaced abomasum. All cows enrolled in the study were assessed for the presence of purulent vaginal discharge (PVD; Dubuc et al., 2010) once between d 30 and 36 postpartum by visual examination of the tail for purulent debris and vaginoscopy. A diagnosis of PVD was recorded if either of the 2 conditions was present.

Behavior

Feeding and lying behavior measures were collected between January 2010 and January 2011 for a subset of animals. Daily feeding behaviors for the first 2 d following calving were captured for 31 animals from continuous video recording using a wide-angle camera lens (Panasonic camera WV-CP504 and lens WV-LZA61/2S, Panasonic Canada Inc., Mississauga, ON, Canada) connected to a recording system (GeoVision, UVS 1240E2, GeoVision Inc., USAVisionSys, Irvine, CA). Each animal's feeding behavior was analyzed by

an individual blind to treatment and was defined as follows: (1) feeding visit: a visit consisted of the animal inserting her head past the head-gate in the manger up to her withers until the animal removed her head from the head-gate completely; and (2) total feeding time: the total amount of time (min) that the animal spent with her head through the head-gate up to the withers without being locked up in the head-gate for other reasons (e.g., for milking, for treatment, or for blood sampling). Total daily lying time and the number of transitions from standing to lying (or vice versa) were recorded using a 3-axis accelerometer (Hobo Pendant G loggers, Hoskin Scientific Ltd., Burnaby, BC, Canada; validation of this device can be found in Ledgerwood et al., 2010) attached to the right hind leg, on the day that each animal ($n = 38$) entered the maternity pen, and recording at 1-min intervals. Lying behavior for the first 3 d following calving was analyzed.

Statistical Analysis

Because there were no existing data at the time of trial planning to inform expected production effects, sample size was estimated based on a combination of practicality of achieving the desired number of dystocic cows in a reasonable time from our research dairy and effects on important production parameters that were both detectable and relevant for the industry. Based on the year prior to the start of this study, we expected that 100 dystocic cows could be enrolled in this study, which would take between 12 and 24 mo depending on the incidence of dystocia. Data for the sample size calculations (mean $\pm$ SD) were based on previous studies conducted at the Elora Dairy Research Center. Sample size was therefore calculated for treatment groups ($n = 48$ per group) based on detection of a difference of 2.4 kg of milk production with an SD of 3.6 kg and a difference of 0.50 kg of DMI with an SD of 0.75 kg/d for the first 14 DIM with 95% confidence and 90% power.

Data were stored in a spreadsheet using Microsoft Office Excel (2010, Microsoft Corp., Redmond, WA) and all descriptive statistics and analyses were performed with Stata Intercooled 10.1 (StataCorp, College Station, TX). Mixed multivariable models were built including a random intercept for animals to account for multiple measurements being taken from each cow. Mixed linear regression models were for the outcomes of DMI, milk production, and serum metabolites (BHBA, NEFA, glucose, calcium, and haptoglobin). Linear regressions were used for the BW differences from calving to 60 d postcalving and for feeding behavior (visit numbers, total time at the feed bunk, and DMI). A logistic regression model was used for the bi-

nary outcome of presence or absence of PVD. All tests were 2-sided and significance was based on $\alpha < 0.05$. For all outcomes, each predictor variable was screened individually and offered to the multivariable model if $P < 0.20$. Variables were kept in the final model if $P < 0.05$ if they acted as a confounder or were part of a significant interaction term. A confounder variable was defined as a nonintervening variable whose inclusion in the model made a 20% or greater change in the coefficient of significant variables in the final model (Dohoo et al., 2003). Interactions between treatment and any significant covariates in the final model were tested. Linearity of predictors was assessed using a lowess (locally weighted scatterplot smoothing) curve for the continuous independent variables. If the linearity assumption was violated, the continuous outcome was transformed, or a quadratic term was included in the model, or the variable was categorized. To account for the curvilinear relationship between haptoglobin and time, a quadratic term was added to the model. The treatment variable was retained in all models, and time was forced into all mixed models.

We examined standardized residuals at the observation level to identify outliers for the linear and mixed linear regression models. For identification of outliers in the logistic model Pearson and deviance residuals were examined. In all random effect models we examined BLUPs for any outliers. Normality and homogeneity of variance were assessed for the observation-level standardized residuals for mixed linear models, and BLUPs were examined for the cow-level models. A Pearson goodness-of-fit test was performed for the regular logistic regression model for the PVD outcome.

RESULTS

BW

The mean ($\pm$ SD) BW before calving for heifers was 588 kg $\pm$ 19 and for cows was 699 kg $\pm$ 21. Treatment groups did not differ in BW change from calving to 60 DIM ($\beta = 2.5$ kg; $P = 0.80$; 95% CI: $-17.6, 22.7$); however, we did observe a decrease in BW at 60 DIM compared with calving ($\beta = -34.4$ kg; $P < 0.001$; 95% CI: -43.3 to -25.6).

Feed Intake and Milk Production Data

Final regression models for DMI and milk production are summarized in Table 1. We observed no differences between meloxicam and placebo groups in DMI (overall mean $\pm$ SD, 12 ± 3 kg/d) or milk production (22 ± 8 kg/d) over the first 14 DIM (Table 1). Both DMI and milk production increased over the first 14 d and heifers ate less and produced less milk than multiparous cows (Table 1). Animals that had retained fetal membranes produced less milk (Table 1) compared with animals that expelled their fetal membranes within the first 24 h.

Blood Analysis

The meloxicam and placebo groups did not differ for any of the serum metabolites measured. Although we found time and parity effects for BHBA and NEFA, we found no effect of having retained fetal membranes. Cows with retained fetal membranes had higher haptoglobin concentrations ($\beta = 0.25$ g/L; $P < 0.05$; 95% CI: 0.07, 0.42).

Table 1. Mixed linear regression models of feed DMI from calving to 14 d postpartum and milk production from calving to 14 d postpartum for 100 Holstein cows with assisted calving randomly assigned to receive meloxicam (0.5 mg/kg of BW once) or placebo approximately 24 h after calving

Fixed effect	Variable	DMI (kg/d)			Milk production to 14 DIM (kg/d)		
		β^1	<i>P</i> -value	95% CI	β	<i>P</i> -value	95% CI
Treatment	Meloxicam	0.52	0.30	$-1.5, 0.5$	-0.35	0.73	$-1.7, 2.4$
	Placebo	Ref. ²			Ref.		
Time	Day	0.31	<0.001	$0.28, 0.34$	1.2	<0.001	$1.1, 1.3$
Parity	Heifer	-2.0	0.01	$-3.4, -0.59$	-6.8	<0.001	$-9.7, -3.9$
	Cow	Ref.			Ref.		
RP ³	BW at calving (kg)	0.01	0.01	$0.00, 0.02$	0.03	0.001	$0.01, 0.05$
	RP	—	—	—	-3.9	0.004	$-6.5, -1.3$
	No RP	—	—	—	Ref.	—	—
	Intercept	4.8	—	$-1.2, 10.9$	3.2	—	$-9.5, 15.8$
Random effect	Level	Variance	SE		Variance	SE	
	Cow	6.0	0.19		23.9	0.39	
	Observation	4.0	0.04		25.3	0.11	

¹Model coefficient.

²Referent.

³RP = retained fetal membranes; RP covariate was not included in the DMI model because it was not significant.

Health Events

Rectal temperature ($38.8^{\circ}\text{C} \pm 0.61$ SD) did not differ ($P = 0.84$) over the first 10 DIM between treatment groups, and the odds of PVD did not differ between treatment groups at 30 to 36 DIM (odds ratio = 1.2; $P = 0.83$).

Lying and Feeding Behavior

Animals in the meloxicam group visited the feed bunk more often than those in the placebo group in the 24 h following treatment (52 ± 56 SD and 28 ± 13 SD, respectively; Table 2). Similarly, the total time spent feeding for meloxicam-treated animals was greater than for animals in the placebo group ($223.4 \text{ min} \pm 112.8$ SD and $156.6 \text{ min} \pm 73.0$ SD, respectively; Table 2).

Total daily lying time ($666.9 \text{ min} \pm 182.5$ SD), number of lying bouts (14.5 ± 5.2 SD), and average lying time per bout ($51.2 \text{ min} \pm 21.4$ SD) over the first 3 d postcalving were not different between treatment groups ($P > 0.05$).

DISCUSSION

The administration of meloxicam subcutaneously 24 h following assisted parturition in Holstein cows failed to improve DMI or milk production for the first 14 DIM. Treatment with NSAIDs has been shown to improve DMI in calves following dehorning or after developing diarrhea (Heinrich et al., 2010; Todd et al., 2010). In the study by Heinrich et al. (2010), calves treated with meloxicam following cautery dehorning had a tendency to consume more feed on d 1 than on d 0 compared with control calves. In the study by Todd et al. (2010), meloxicam-treated calves that developed diarrhea and were enrolled after 10 d of age had greater odds of consuming all of the offered milk compared with placebo-treated calves of the same age with di-

arrhea. Furthermore, calves treated with meloxicam began consuming starter ration earlier than placebo-treated calves (Todd et al., 2010). On the other hand, oral meloxicam did not have any effect on DMI when given to beef calves that were castrated upon arrival at the feedlot compared with steers (Coetzee et al., 2012). Richards et al. (2009) did not find any effects of ketoprofen administration following calving on milk yield. Similarly, Duffield et al. (2009) and Shwartz et al. (2009) did not find any effect of flunixin meglumine on milk yield following calving. We also observed no treatment differences in metabolic indicators over the first 12 d or in the probability of PVD at 5 wk after calving.

The decision to treat at 24 h was made to ensure that meloxicam would not interfere with the prostaglandin response that may contribute to uterine contractions to expel fetal membranes (Horta, 1984). Duffield et al. (2009) reported an increase in the odds of having retained fetal membranes in animals that received flunixin meglumine approximately 2 h after calving. Similarly, Waelchli et al. (1999) reported a high probability of retained fetal membranes in cows administered flunixin meglumine following a caesarean section. On the other hand, treatment with 2 doses of ketoprofen, one immediately following calving and the second 24 h later, tended to reduce the incidence of retained fetal membranes in dairy cows (Richards et al., 2009). The potential for retained fetal membranes using an NSAID was the main reason why we waited 24 h before administering treatment. The NSAIDs act on cyclooxygenase enzymes COX-1 and COX-2, which in turn mediate prostaglandin production (Lees et al., 2004). Different NSAIDs have different affinities for COX-1 and COX-2, and the exact mechanism of NSAID on retained fetal membranes has not yet been determined. However, the 24-h delay in treatment administration may explain the lack of a treatment effect in the current study. Given

Table 2. Linear regression models for feeding behaviors and DMI for 24 h after injection controlling for baseline (the period from calving to time of treatment) for 31 animals with assisted calving and randomly assigned to receive meloxicam (0.5 mg/kg of BW), or placebo, by subcutaneous injection approximately 24 h after calving

Fixed effect	Variable	Number of visits			Time at the feed bunk (min)			DMI (kg)		
		β^1	<i>P</i> -value	95% CI	β	<i>P</i> -value	95% CI	β	<i>P</i> -value	95% CI
Treatment	Meloxicam	11.5	0.003	4.4, 18.5	40.3	0.04	2.9, 77.7	0.13	0.83	−1.1, 1.4
	Placebo	Ref. ²			Ref.			Ref.		
Baseline		0.34	0.02	0.07, 0.62	0.39	0.02	0.07, 0.71	0.57	<0.001	0.32, 0.81
Parity ³	Heifer	—	—	—	—	—	—	−1.7	0.033	−3.2, −0.14
	Cow	—	—	—	—	—	—	Ref.		
Intercept		29.0	—	20.0, 38.0	132.1	—	82.1, 182.2	6.7	—	3.2, 10.2

¹Model coefficient.
²Referent.
³Parity covariate was not included in the number of visits and time at feed bunk models because it was not significant.

that the placental separation process usually takes less than 6 h (van Werven et al., 1992), future investigations should consider administering meloxicam sooner (i.e., immediately following calving) to examine the risk of retained fetal membranes and ability to mitigate pain from calving.

Cows that received meloxicam spent more time at the manger on the day after treatment, although DMI did not differ in the 24 h after injection. The increased number of feeding visits and total time spent feeding for the first 24 h after calving in the meloxicam-treated animals suggests that administration of this NSAID could be alleviating some postcalving pain. Similarly, Theurer et al. (2012) reported that meloxicam-treated calves spent significantly more time with 1 foot from the grain bunk on d 2 and 5 following dehorning compared with control calves, suggesting a potential positive effect of meloxicam on behavioral changes following a painful procedure. Other work has shown that lame cows at pasture grazed for shorter periods and had longer lying times than nonlame cows (Hassall et al., 1993; Winckler and Brill, 2004). Cows that received ketoprofen following left displaced abomasum surgery had greater odds of going to the feed bunk at fresh feed delivery for the first 3 d postsurgery compared with control animals based on observations by producers blinded to treatment (Newby et al., 2013). Improved DMI in dairy cows should improve milk yield, as intake and production are closely related, and potentially reduce the risk of disease (Drackley, 1999). Because this was not observed in the current study, the potential benefits may have been masked by the elevated endorphins still in the blood following parturition (Hydbring et al., 1999). Perhaps the cows that received meloxicam and spent more time at the feed bunk ate smaller but more frequent meals. Further research is needed to investigate the effects of longer term NSAID administration, or a higher dosage of NSAID, on feeding behavior because return to a more normal feeding behavior may improve rumen health with smaller and more frequent meals (Krause and Oetzel, 2006). The present study was done in a noncompetitive environment for the cows, where they had access to their own feed bunk. It would be interesting to investigate the potential benefits of meloxicam administration following calving on the feeding behavior of cows in a freestall system.

In the present study, the lack of effect of meloxicam on DMI, milk production, blood parameters, or lying behavior following an assisted calving could be due to insufficient attenuation of inflammation or pain or because the duration of effect of the meloxicam regimen used in this study was too short. Conversely, the differences in feeding behavior suggest that effects were

produced and that further investigation of antiinflammatory treatment strategies is warranted.

CONCLUSIONS

This is one of the first studies to investigate the effects of administering the NSAID meloxicam following assisted calving. We observed no differences associated with treatment in DMI, milk production, or metabolic indicators. These outcomes may not have been sensitive to the effect of the drug or the dose regimen used in this study. We did observe short-term effects on feeding behavior that merit further investigation. We recommend future research to investigate different analgesic strategies (different dose, timing, and duration of meloxicam, and different drugs) to mitigate the effects of assisted calving.

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