Clinical impacts of administering a nonsteroidal anti-inflammatory drug to beef calves after assisted calving on pain and inflammation, passive immunity, health, and growth

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ABSTRACT: Assisted calves are often born weak, injured, or oxygen deprived and have a higher risk of morbidity and mortality. The objective was to investigate the impact of using pain mitigation at birth in assisted beef calves on physiological indicators of pain and inflammation, passive immunity, health, and growth. Thirty-three primiparous cows and their calves requiring assistance at birth on two ranches located in southern Alberta were enrolled. Data collected at birth include date and time of calving, calf sex, meconium staining, presentation of calf, and calving difficulty (easy assist: one person manually delivered the calf; difficult assist: delivery by two or more people, or mechanical assistance). Within 10 min of birth, calves were stratified by calving difficulty, randomized to a medication group, and received a subcutaneous dose of meloxicam (0.5 mg/kg BW) or an equivalent volume of placebo. Cow–calf pairs were then placed in individual box stalls for observation and sampling. At birth, 1, 4, and 24 h after birth, heart rate, respiratory rate, and rectal temperature were assessed and blood samples collected to measure indicators of pain and inflammation (cortisol, corticosterone, substance P, and haptoglobin). Serum IgG concentration and failed transfer of passive immunity (serum IgG concentration <24 g/L) were assessed in the 24-h blood samples. Preweaning treatment for disease and mortality information was collected and calves were weighed at 7 to 10 d of age and at weaning. Of the 33 calves enrolled, 17 calves received meloxicam and 16 calves received a placebo. Meloxicam-medicated calves had significantly greater ADG to 7 to 10 d of age ($P = 0.05$) (mean = 0.9 kg/d; SE = 0.10) compared with placebo-medicated calves (mean = 0.6 kg/d; SE = 0.12). There was no significant effect of meloxicam on physiological indicators of pain and inflammation, standing or nursing by 1 h, passive immunity, health outcomes, or ADG to weaning ($P > 0.1$). Although this was a small sample population, meloxicam given to assisted calves at birth improved ADG in the first week of life, which may indicate an important production management tool for improving well-being in assisted calves.

Key words: beef cattle, calving difficulty, growth, meloxicam, neonates, pain

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INTRODUCTION

Calf health and survival are predominant concerns of cow–calf producers (Murray et al., 2016a). An important factor that affects calf health and survival is the difficulty experienced during the birthing process (Sanderson and Dargatz, 2000; Mellor and Stafford, 2004). Assisted calving is when a decision is made to intervene and deliver a calf and a degree of difficulty may be assigned to that calving (Mee, 2008). Incidence of assisted births in beef cows ranges from 5% to 20% in heifers and 1% to 4% in mature cows in North America (Dargatz et al., 2004; NAHMS, 2009; Waldner, 2014). Assisted calves have a higher risk of trauma and oxygen deprivation, and are less vigorous (Ferguson et al., 1990; Bleul and Gotz, 2013; Homerosky et al., 2017a). This can lead to delayed colostrum consumption (Mellor and Stafford, 2004; Homerosky et al., 2017b). Inadequate ingestion of good quality colostrum leads to failed transfer of passive immunity, which is associated with preweaning morbidity, mortality, and lower ADG (Wittum and Perino, 1995; Dewell et al., 2006). Further, dystocias are considered extremely painful for the cow and calf (Huxley and Whay, 2006; Mainau and Manteca, 2011; Barrier et al., 2012b). Nonsteroidal anti-inflammatory drugs (**NSAIDs**) are increasingly being used for cattle pain management (Murray et al., 2016a; Moggy et al., 2017). Practical strategies that can mitigate effects of a difficult calving and improve transfer of passive immunity are important to ensure calf health and survival and optimize profit for cow–calf producers. Therefore, the objective was to investigate the impact of implementing pain mitigation at birth to assisted beef calves. The hypothesis was that administering meloxicam at birth to assisted calves would decrease pain and inflammation, improve transfer of passive immunity, decrease the risk for morbidity and mortality, and increase growth.

MATERIALS AND METHODS

The study was approved by the University of Calgary Veterinary Sciences Animal Care Committee (AC15-0150) and was conducted in accordance with guidelines established by the Canadian Council on Animal Care. Sample size calculations were based on previous work by this group looking at physiological indicators of trauma in calves at 24 h of age in relation to calving score (Pearson et al., 2019). A sample size of 16 calves per medication group was deemed necessary to detect a significant difference between the mean values of aspartate aminotransferase, an indicator of muscle trauma, in unassisted (mean = 61.9 IU/L; SD = 14.4) and difficult assisted calvings (mean = 92.3 IU/L; SD = 37.1) based on a significance level of 0.05 and 80% power. The data were collected from January to May of 2016 on two cow-calf operations located in southern Alberta, Canada. The operations were selected based on relationships with local cow–calf veterinary consultants, number of heifers to calve, and proximity to the University of Calgary. Thirty-three primiparous dams (ranch A = 20; ranch B = 13) were enrolled in the study. Eligible dams on ranch A consisted of 185 primiparous dams (either purebred registered Angus or crossbred commercial cattle) and on ranch B consisted of 150 crossbred primiparous dams. On both ranches, pregnant dams were monitored in outdoor precalving pens close to the calving barn and checked hourly for signs of calving. On ranch A, during cold weather, the majority of dams were brought into a heated barn with individual, 12 ft. × 12 ft. stalls bedded with straw. One dam on ranch A was recumbent and unable to walk to the barn during calving so was assisted outside in the precalving pen. On ranch B, dams were allowed to calve outside unless they required assistance. Dams were observed either by camera surveillance (GoPro Hero3+, GoPro Inc., San Mateo, CA) or by visual surveillance from a distance for signs of impending parturition. Failure to calve or make progression within 1 to 2 h of estimated onset of stage 2 labor (e.g., amniotic sac visible, feet present, strong abdominal contractions, etc.) resulted in the dam being moved into a chute for vaginal examination and delivery of the calf. Twins and deliveries by Caesarian-section were excluded from this study.

Data collected at the time of birth include date and time of calving, ambient temperature, calf sex, meconium staining, presentation of the calf (anterior vs. posterior), and calving difficulty. Calving difficulty was classified as either an easy assist (one person pulling to deliver the calf) or difficult assist (two or more people pulling to deliver the calf or mechanical assistance). Within 10 min of birth, a physical examination and evaluation of calf vigor were performed as described by Homerosky and colleagues (2017a,b). Mucous membrane color was categorized into normal (light pink or dark pink) or abnormal (blue-purple, white, and dark red) by visual examination of the oral mucous membranes. Tongue withdrawal was categorized as complete or incomplete when the tongue was pulled from the calf's mouth and the extent to which it withdrew the tongue back into its mouth determined. Suckle reflex was categorized as strong or weak by placing a finger in the calf's mouth and feeling if it suckled the finger. These vigor parameters are associated with acidemia (Homerosky et al., 2017a) and likelihood of a calf standing to nurse on its own within 4 h after birth (Homerosky et al., 2017b). The presence of meconium staining (yes or no), heart rate, respiratory rate, and rectal temperature were also recorded at birth. Calves were transported in a calf sled to a digital scale to measure the birth weight of the calf.

Assisted calves were randomized to a medication group using a computer-assisted randomization chart (Microsoft Excel, Microsoft Corporation, Redmond, WA) stratified by calving difficulty (easy assist or difficult assist). Calves received a subcutaneous dose of meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or an equivalent volume of placebo (sterile saline with 2% oxytetracycline [Oxymycine LP, 100 mg/mL, Zoetis Canada Inc., Kirkland, QC] to match the color of meloxicam). The amount of oxytetracycline that would be injected was 4.4×10^{-6} mg/kg BW, which is a small fraction of the concentration of therapeutic oxytetracycline (6.6 mg/kg BW) and would likely not impact the results of this study. Ranch and research personnel were blinded to the treatment group. On-farm protocol dictated that all dams assisted at calving received meloxicam (Meloxicam Oral Suspension, 15 mg/mL, 1.0 mg/kg BW, Bow Valley Research, Calgary, AB at ranch A; Metacam injectable solution, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany at ranch B).

Sampling time points for all calvings enrolled included: birth (within 10 min of delivery), 1, 4, 24 h, and 7 to 10 d post-delivery. All calves had blood drawn from the jugular vein by vacutainer needle (20-gauge × 1 in.; Airtite Product Co. Inc., Virginia Beach, VA). At each time point, blood was collected into a vacutainer (BD Vaccutainer, BD, Franklin Lakes, NJ) coagulation tube (10 mL), EDTA tube (6 mL), and heparinized tube (10 mL). After blood collection, a drop of heparinized whole blood was placed on a lactate strip and analyzed immediately for L-lactate concentrations (Lactate Pro, Arksay, Japan; or Lactate Plus Meter, Nova Biomedical, Watham, MA). Each EDTA tube had 300 μL of benzamidine hydrochloride (Sigma-Aldrich, St. Louis, MO) solution (a protease inhibitor) added and was inverted 10 times to mix. Heparinized and EDTA tubes were then centrifuged at $3{,}000 \times g$ for 10 min (LW Scientific E8, Lawrenceville, GA). Coagulating tubes were allowed to clot first and then centrifuged for 20 min at $3{,}000 \times g$. Serum or plasma were removed from blood collection tubes, placed in 2 mL cryotubes, and immediately frozen at −18 °C. Once a week, samples were transported to the University of Calgary Faculty of Veterinary Medicine and placed in a −80 °C freezer until further analysis.

After the at-birth examination and sampling, cow-calf pairs were placed in individual box stalls for observation and sampling until after the 24-h sample collection. Latency to stand and nurse were recorded and if the calf had not sucked within 1 to 4 h, the on-farm protocol recommended calves be bottle- or tube-fed 1 L of maternal colostrum or colostrum replacer (Calf Choice Total, Saskatoon Colostrum Co. Ltd, Saskatoon, SK at ranch A; ImmuStart 50, Imu-Tek, Fort Collins, CO at ranch B). The cow–calf pairs were then moved to an outside pen measuring ~30 × 30 m to be observed by the ranch personnel.

At 7 to 10 d of age, calves were restrained in a calf chute with a built-in scale (7L Livestock Equipment Ltd., Brandon, MB) for BW measurement and blood collection.

Table 1 summarizes the parameters evaluated at the different sampling times. Serum cortisol and corticosterone concentrations were measured by an Agilent 1200 binary liquid chromatography system connected with an AB SCIEX QTRAP 5500 tandem mass spectrometer equipped with electrospray ionization source in the Wynne-Edwards Research Lab at the University of Calgary (Calgary, AB). Haptoglobin concentrations were measured by photometric analysis using the Roche Cobas 6000 c501 biochemistry analyzer (Laval, QC) in the Animal Health Laboratory at the University

Table 1. Age of the calf when parameters were evaluated in 33 beef calves assisted at delivery and randomly assigned to a subcutaneous meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 mL/kg) medication group at birth

At-birth	1 h	4 h	24 h	7 to 10 d	Weaning
BW				BW	BW
Cortisol	Cortisol	Cortisol	Cortisol		
Corticosterone	Corticosterone	Corticosterone	Corticosterone		
Substance P	Substance P	Substance P	Substance P		
Heart rate	Heart rate	Heart rate	Heart rate		
Respiratory rate	Respiratory rate	Respiratory rate	Respiratory rate		
Rectal temperature	Rectal temperature	Rectal temperature	Rectal temperature		
L-Lactate			L-Lactate		
Haptoglobin			Haptoglobin	Haptoglobin	
			Serum IgG		
			Serum chemistry		
					Treatment
					Mortality

of Guelph (Guelph, ON). Substance P concentrations were measured by RIA in the Pharmacology Analytical Support Team Laboratory at the Iowa State University, Veterinary Diagnostic Laboratory (Ames, IA) as described by Van Engen et al. (2014). Serum IgG concentrations were measured using an in-house RIA in the Quality Assurance Laboratory of the Saskatoon Colostrum Company Ltd. (Saskatoon, SK) as described by Chelack et al. (1993). Serum biochemistry profile analysis was performed on a Beckman AU680 chemistry panel machine (Beckman/Coulter, Mississauga, ON) at the IDEXX Reference Laboratories (Calgary, AB). The concentration of plasma meloxicam was measured in heparinized blood samples using high performance liquid chromatography (Shimadzo LC-10A, Shimadzu Scientific Instruments, Columbia, MD) and was performed as described by Vivancos et al. (2015). Meloxicam concentrations were assessed in samples from meloxicam-treated calves on both ranches to ensure therapeutic levels were reached when it was administered to neonatal calves at birth. It was also measured in the samples from placebo-treated calves on both ranches to determine if they had absorbed any meloxicam through the milk because all dams were treated with meloxicam after calving.

Treatment and mortality data of all calves enrolled were recorded by ranch personnel. Date, suspected disease, and drugs used were recorded for treatment of disease in the preweaning period. Calves that died during the preweaning period were submitted to the University of Calgary Faculty of Veterinary Medicine Diagnostic Services Unit for gross and histological examination. Individual weaning weights were collected on calves at weaning.

Data were analyzed using STATA 14.1 software (StataCorp LP, College Station, TX) to investigate the relationships of medication group (placebo vs. meloxicam) with physiological indicators of pain and inflammation, passive immunity, and calf health and growth. Descriptive statistics were performed on all variables and tests for normality were also performed on continous variables. Multicollinearity was assessed using Spearman's rank correlation. Exact logistic regression was used to evaluate: failed transfer of passive immunity (determined using <24 g/L of serum IgG as a cut-point), standing by 1 h, nursing by 1 h, treatment, and mortality in the preweaning period. Multivariable linear regression modeling was performed for the following outcome variables: serum IgG concentration, 24-h L-lactate, 24-h haptoglobin, 7- to 10-d haptoglobin, 7- to 10-d ADG, and weaning ADG. ADG was calculated by subtracting the birthweight of the calf from the measured weight and dividing by the age (in days) of the calf at the time of the measured BW. Mixed multivariable linear regression modeling for repeated measures was performed for the following outcome variables: cortisol, corticosterone, substance P, heart rate, respiratory rate, and rectal temperature. Ranch, calving difficulty, and at-birth parameters of the corresponding outcome variable were offered as fixed effects to the models. Calf was offered as a random effect in the repeated measures models. Passive immunity models (i.e., serum IgG concentration and failed transfer of passive immunity) also had route of

colostrum administration (nursed from dam or assisted by bottle or esophageal tube) and type of colostrum (dam colostrum or colostrum replacement product) offered as covariates. Birthweight, serum IgG concentration, and failed transfer of passive immunity were offered as potential covariates to the treatment for disease and mortality models. In addition, treatment for disease was offered to the ADG models. All models were analyzed using forward selection model building strategies. Non-significant terms were removed, except for medication group, which was forced into the model because it was the variable of interest. Additionally, partial F-tests were used when categorical variables were removed from the models. The significance level to be retained in the model was set at $\alpha = 0.05$. Models were checked for assumptions by Cook–Weisberg test for heteroscedasticity and Shapiro–Wilk W test for normality. Residuals were assessed visually by residual-vs.-fitted plots. Outliers and leverage were assessed using Cook's distance, as well as the DFIT and DFBETA tests for influential observations. Individuals that were outliers or leveraged the model were removed and the data reanalyzed to determine if the resulting model was different. If the models were the same, the individual remained in the model. Models that did not fit the assumptions had variables transformed for normal distribution, using a transformation selected by visual assessment of several transformations determined by using the "gladder" command. All significant covariates were checked for interactions within each model. Two-sample T tests were performed to compare 24-h hepatic enzymes (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) and renal biochemical parameters (urea and creatinine) between meloxicam and placebo groups to assess impacts of the medication on hepatic and renal function.

RESULTS

Eleven of the enrolled births were easy assists and 22 were difficult assists. Only one difficult assisted calf presented posteriorly. One of the 22 difficult assist calves was delivered manually by two or more people. The others were all delivered by mechanical traction. Six of the 22 difficult assisted calves had meconium staining at birth. None of the easy assist calves had meconium staining. Seventeen calves received meloxicam and 16 calves received placebo. Table 2 describes the demographics of calves enrolled in the study by medication group.

Table 2. Demographics of 33 beef calves by medication group[1]

	Placebo	Meloxicam	Overall
Ranch			
A	10	10	20
B	6	7	13
Breed			
Angus	5	7	12
Crossbred	11	10	21
Calf sex			
Bull	12	13	25
Heifer	4	4	8
Meconium staining			
No	11	16	27
Yes	5	1	6
Ambient temperature, ºC (median, IQR)	10.0 (6.9 to 11.1)	11.7 (10 to 12.2)	10.9 (9.4 to 11.7)
Birthweight, kg (mean, SD)	39.9 (5.4)	39.6 (8.1)	39.8 (6.8)

[1]Calves were administered a dose of either subcutaneous meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 mL/kg) at birth. All parameters are presented as counts unless otherwise stated.

The average meloxicam concentration in meloxicam-treated calves at birth, 1, 4, and 24 h were no detectable levels of meloxicam, 2,957.8 ng/mL (SD = 3,080.2), 2,429.3 ng/mL (SD = 485.6), and 1,696.0 ng/mL (SD = 488.9), respectively. Placebo-treated calves did not have detectable levels of meloxicam at birth, 1 h, and 4 h of age. At 24 h, seven of the 16 placebo treated calves (5/10 from ranch A and 2/6 from ranch B) had low levels of detectable meloxicam in the serum (mean = 15.4 ng/mL; SD = 17.9), which could only have been absorbed from the dam's milk.

The majority of vigor parameters were normal by 1 h, so this precluded further analysis aside from describing the at-birth vigor parameters prior to product administration. Twenty-one of 33 calves had weak suckle reflexes at birth, eight of 33 had incomplete tongue withdrawal reflexes, and seven of 33 had abnormal mucous membrane colors. Five of the 33 (15%) calves were treated for disease in this study (meloxicam group: $n = 1$; placebo group: $n = 4$). Six of the 33 (18%) calves died prior to weaning (meloxicam group: $n = 3$; placebo group: $n = 3$).

There were no significant differences ($P \geq 0.17$) between meloxicam-treated and placebo-treated calves for 24-h ʟ-lactate, 24-h haptoglobin, and 7- to 10-d haptoglobin. Table 3 reports these models, including the significant covariates. Similarly, there were no significant differences between medication groups ($P \geq 0.12$) when comparing repeated

Table 3. Multivariable linear regression models of blood physiological parameters of acidemia or inflammation in 33 beef calves assisted at birth and medicated with subcutaneous meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 mL/kg)

	Coefficient	Standard error	*P*-value
24-h l-lactate, mmol/L			
Medication group			
Placebo	Referent	—	—
Meloxicam	−0.4	0.4	0.41
Birth L-lactate, mmol/L	0.2	0.07	0.02
24-h haptoglobin, g/L[a]			
Medication group			
Placebo	Referent	—	—
Meloxicam	0.06	0.04	0.17
Birth haptoglobin, g/L	4.4	0.7	<0.0001
7- to 10-d haptoglobin, g/L[b]			
Medication group			
Placebo	Referent	—	—
Meloxicam	3.6	8.0	0.66
Ranch*			
A	Referent	—	—
B	−22.2	8.5	0.01

[a]Log transformation.

[b]$1/x^2$ transformation.

*Due to the transformation, the sign is reversed (ranch A had lower 7- to 10-d haptoglobin than ranch B).

measures of cortisol, corticosterone, substance P, heart rate, and rectal temperature over the 24-h period. Table 4 reports the mixed multivariable linear regression repeated measure models for cortisol, corticosterone, substance P, heart rate, respiratory rate, and rectal temperature, including significant covariates. Respiratory rate was significantly associated with medication given ($P = 0.025$) when taking into account an interaction between medication group and calving difficulty. The only significant pairwise comparison was between placebo-treated easy and difficult assisted calves ($P = 0.02$): easy assists receiving a placebo had a mean respiratory rate of 46.0 bpm (SE = 3.49) while difficult assists receiving a placebo had a mean respiratory rate of 55.0 bpm (SE = 1.83). Overall, the means for placebo and meloxicam treated calves' respiratory rates were 52.2 bpm (SE = 1.75) and 51.1 bpm (SE = 1.59), respectively, which was not significantly different ($P = 0.6$). The raw means (SD) for each pain or inflammatory mediator by medication group can be found in the supporting document (Table 6).

The odds of standing by 1 h, nursing by 1 h, and having failed transfer of passive immunity, and serum IgG concentrations were not significantly different between placebo and meloxicam medicated groups ($P \geq 0.18$), as reported in Table 5. Preweaning treatment and mortality risk were not significantly different between calves medicated with a placebo or meloxicam ($P \geq 0.31$). Meloxicam-treated calves had significantly higher ADG to 7 to 10 d of age ($P = 0.05$; mean = 0.9 kg; SE = 0.10), compared with placebo-treated calves (mean = 0.6 kg; SE = 0.12). Serum IgG concentration and ranch were also important factors associated with ADG to 7 to 10 d (Table 5). ADG to weaning was not statistically different in meloxicam-treated calves compared with placebo-treated calves when taking into account an interaction between ranch and treatment for disease (Table 5).

There was no significant difference between meloxicam and placebo treated calves on hepatic enzymes and renal biochemical parameters (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, urea, and creatinine) ($P \geq 0.22$).

DISCUSSION

The pain calves experience during calving is a topic of increasing interest in the beef industry (Laven et al., 2012). In a study of beef producers in Alberta in 2013, only 13% of surveyed beef producers reported using a pain medication in newborn calves after dystocia and 15% in the cows (Murray et al., 2016a). More recently, Moggy and colleagues (2017) stated that 28% and 33% of beef producers in western Canada reported giving an NSAID after dystocia to the calf and cow, respectively. Nonsteroidal anti-inflammatory drugs provide a multimodal relief by analgesic, anti-inflammatory, and anti-endotoxic effects (Coetzee, 2013). Meloxicam is an NSAID with high bioavailability and a prolonged half-life, making it a favorable choice for treating pain in cattle (Coetzee, 2013). Therefore, the hypothesis for this study was that administering meloxicam at birth to assisted calves would decrease pain and inflammation, improve transfer of passive immunity, decrease the risk for morbidity and mortality, and increase growth. Although NSAIDs are designed to decrease pain and inflammation (Coetzee, 2011), no association was found in the measured physiological indicators of pain and inflammation between meloxicam and placebo medicated calves in the present study and our hypothesis was not supported. This is in agreement with recent work investigating the effects of another NSAID, ketoprofen, on stress biomarkers in calves (Gladden et al., 2018). In that

Table 4. Mixed linear regression repeated measures models of blood parameters and physical examination findings associated with pain or inflammation in 33 beef calves assisted at birth and medicated with subcutaneous meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 mL/kg)

	Coefficient	Standard error	P-value
Cortisol, ng/mL			
Medication group			
Placebo	Referent	—	—
Meloxicam	−1.7	3.6	0.62
Ranch			
A	Referent	—	—
B	−22.8	14.5	0.11
Calving difficulty			
Easy	Referent	—	—
Difficult	7.6	3.9	0.05
At-birth[a] cortisol	−0.7	0.4	0.08
Time sampled			
1 h	Referent	—	—
4 h	−20.9	3.5	<0.0001
24 h	−48.4	3.5	<0.0001
Farm by at-birth[a] cortisol interaction	0.4	0.2	0.009
Corticosterone,[b] ng/mL			
Medication group			
Placebo	Referent	—	—
Meloxicam	0.2	0.1	0.122
Ranch			
A	Referent	—	—
B	0.3	0.1	0.021
At-birth[a] corticosterone	0.4	0.06	<0.0001
Time sampled			
1 h	Referent	—	—
4 h	−1.1	0.2	<0.0001
24 h	−1.8	0.1	<0.0001
Substance P,[c] pg/mL			
Medication group			
Placebo	Referent	—	—
Meloxicam	−0.002	0.0001	0.20
At-birth[a] substance P	−0.0001	0.00002	<0.0001
Time sampled			
1 h	Referent	—	—
4 h	−0.02	0.004	<0.0001
24 h	−0.03	0.003	<0.0001
Heart rate,[d] bpm			
Medication group			
Placebo	Referent	—	—
Meloxicam	−0.3	0.2	0.23
Time sampled			
1 h	Referent	—	—
4 h	−0.5	0.2	0.02
24 h	−0.8	0.2	<0.0001

Table 4. *Continued*

	Coefficient	Standard error	P-value
Respiratory rate, bpm			
Medication group			
Placebo	Referent	—	—
Meloxicam	17.9	8.0	0.02
Calving difficulty			
Easy	Referent	—	—
Difficult	12.5	3.4	<0.0001
Time sampled			
1 h	Referent	—	—
4 h	−0.6	2.1	0.77
24 h	3.0	3.1	0.32
Calving difficulty by medication interaction	−10.5	4.6	0.02
Rectal temperature, C°			
Medication group			
Placebo	Referent	—	—
Meloxicam	0.05	0.1	0.74
Time sampled			
1 h	Referent	—	—
4 h	−0.2	0.1	0.16
24 h	−0.2	0.1	0.10

[a]At-birth refers to baseline measurements of that outcome variable taken within 10 min of birth.

[b]Log transformation.

[c]1/(square root) transformation.

[d]Square root transformation.

study, the authors found no effect of administering an NSAID within 3 h of birth on cortisol, creatine kinase, plasma L-lactate, or total protein concentration at 24 h of age.

Other studies investigating painful management interventions such as castration and dehorning have found a decrease in pain and stress indicators after administering an NSAID (Coetzee, 2011; Stock and Coetzee, 2015). Calves given an NSAID at the time of dehorning had lower substance P than control calves, but there was no difference in haptoglobin or mean serum cortisol levels (Glynn et al., 2013). They also found increased ADG to 7 d after dehorning in medicated calves vs. unmedicated calves. In other meloxicam-specific studies, calves receiving meloxicam in association with dehorning had decreased cortisol, substance P, and prostaglandin E_2 levels, decreased heart rate, and increased ADG to 10 d after dehorning compared with placebo (Coetzee et al., 2012; Allen et al., 2013). In a castration study, substance P levels decreased, but not serum cortisol in calves medicated with meloxicam compared to controls (Coetzee et al., 2008). Contrary to the above

Table 5. Logistic and linear regression models for outcomes associated with passive immunity and ADG in 33 beef calves assisted at birth and medicated with subcutaneous meloxicam (Metacam, 20 mg/mL, 0.5 mg/kg BW, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 mL/kg)

	Odds ratio	P–value
Failure to stand by 1 h		
Medication group		
Placebo	Referent	—
Meloxicam	1	1.0
Ranch		
A	Referent	—
B	13.2	0.003
Failure to nurse by 1 h		
Medication group		
Placebo	Referent	—
Meloxicam	0.7	1.0
Failed transfer of passive immunity		
Medication group		
Placebo	Referent	—
Meloxicam	0.2	0.36
Route colostrum consumed		
Nursed from cow	Referent	—
Tubed or esophageal fed	13.6	0.01
	Coefficient (SE)	**P-value**
Serum IgG, g/L		
Medication group		
Placebo	Referent	—
Meloxicam	6.1 (4.4)	0.176
Calving difficulty		
Easy	Referent	—
Difficult	−14.4 (4.6)	0.004
ADG to 7 to 10 d, kg		
Medication group		
Placebo	Referent	—
Meloxicam	0.29 (0.1)	0.05
Ranch		
A	Referent	—
B	0.4 (0.2)	0.01
Serum IgG concentration, g/L	0.01 (0.005)	0.03
ADG to weaning, kg		
Medication group		
Placebo	Referent	—
Meloxicam	0.05 (0.05)	0.3
Ranch		
A	Referent	—
B	−0.2 (0.06)	0.003
Treatment for disease		
No	Referent	—
Yes	0.5 (0.3)	0.1
Treatment for disease by Ranch interaction	−0.3 (0.1)	0.04

studies, Meléndez et al. (2017) did not find an association between the use of meloxicam before or at the time of castration on substance P or salivary cortisol levels up to 240 min after castration. Together, the results of these studies indicate the complexity of pain physiology and detecting and treating pain in calves.

Serum cortisol and substance P are commonly used biomarkers for the evaluation of analgesic treatments (Coetzee, 2013). Cortisol, as measured by peak concentration or duration, is used as a measure of distress associated with painful stimuli (Mellor et al., 2000). An increase in tractive forces on a calf has been shown to lead to increased levels of cortisol in neonatal calves (Hoyer et al., 1990). Although cortisol is commonly evaluated in pain mitigation studies, it was not significantly different by medication groups in this study. This may be because cortisol is already elevated due to stimulation of the fetal adrenal–pituitary axis to initiate parturition (Breazile et al., 1988). Substance P is a neuropeptide released in response to pain, stress, and anxiety (Coetzee, 2013). Although it has gained popularity in pain mitigation studies, results have not been consistent (Coetzee et al., 2008; Meléndez et al., 2017).

Haptoglobin at 24 h and 7 to 10 d of age was not significantly different by medication group. Murray and coworkers (2014) found no association between calving difficulty and haptoglobin levels but did find higher concentrations of haptoglobin in calves with higher rectal temperatures and depressed attitudes in the first few days after birth. Haptoglobin is an acute phase protein released by the liver after infectious or inflammatory tissue injury (Baumann and Gauldie, 1994). Acute phase proteins are commonly used in veterinary medicine to quantify tissue damage but a lack of significant differences at birth may be due to the immature inflammatory response in the neonate (Alsemgeest et al., 1995; Schroedl et al., 2003)

Other indirect, physiological indicators of pain and inflammation such as heart rate, respiratory rate, and body temperature have been investigated in painful procedures in cattle (Stewart et al., 2010; Coetzee, 2011). Respiratory rate was significantly different by medication group in this study, but the effect was influenced by an interaction between medication and calving difficulty and driven by a significant difference between easy and difficult assists among placebo-treated calves. Although there was a significant difference, the differences were small and deemed not clinically relevant. The normal respiratory rate of the bovine neonate ranges from 36 to 60 bpm (Dufty and Sloss, 1977) and the mean respiratory rate amongst calves medicated with meloxicam or a placebo were within the normal range. Although respiratory rate may be associated with pain, it is also associated with hypoxia,

hypercapnia, and acidemia in neonates, which may confound its relevance in neonatal pain studies (Breazile et al., 1988; Bleul and Gotz, 2013). Heart rate, respiratory rate, and temperature are regulated by the sympathetic nervous system in reaction to pain and therefore a difference might be expected between calves medicated with analgesics vs. controls, as reported in other studies (Mohankumar et al., 2012; Kovacs et al., 2014). Previous work investigating analgesic and anti-inflammatory effects of meloxicam given to calves at the time of a painful procedure has found decreased respiratory rates compared to control calves (Heinrich et al., 2009; Cagnardi et al., 2017).

The effect of an NSAID on appetite and growth has been evaluated in several studies (Todd et al., 2010; Glynn et al., 2013; Murray et al., 2016b). Our hypothesis was that treated calves would be less painful, get up, and nurse more frequently, and therefore gain more weight. Another hypothesis for increased appetite and growth may be due to the decreasing pro-inflammatory cytokine pathways that may affect metabolism and nutrient intake (Johnson, 1998). The only notable impact of administering meloxicam at birth in this study was an increase in ADG to 7 to 10 d. Ranch and serum IgG concentration were significant covariates for ADG to 7 to 10 d of age, indicating that the ranch management and colostrum consumption are also important factors for weight gain in the first week of life. These findings were expected because management practices differed on the two ranches. In addition to immunoglobulin absorption, colostrum contains other important factors that impact calf health such as nutrients, immune cells, growth factors, and antimicrobial properties, which may explain why IgG concentrations (an indicator of colostrum absorption) were associated with weight gain (Godden, 2008).

A difference in ADG between medication groups was not found at weaning. Whether the calves were treated for disease in the preweaning period did affect their ADG to weaning, although this was influenced by which ranch they lived on. In other pain studies, calves that were medicated with meloxicam had greater ADG to 7 to 10 d after dehorning compared with unmedicated calves (Coetzee et al., 2012; Glynn et al., 2013). Murray and colleagues (2016b) investigated the use of meloxicam given to dairy calves at birth and found greater milk intake, better health in the first 8 wk, and greater vigor, but no significant effect on ADG. A similar study (Todd et al., 2010) investigated the impacts of an NSAID given to calves with diarrhea.

They found that calves treated with meloxicam consumed starter ration sooner, had higher odds of finishing daily allotted milk, gained weight at a faster rate, and weaned earlier.

Serum IgG concentrations have been reported to be lower in calves born to a heifer, via dystocia, or as a twin, and the odds of treatment or death increased when serum IgG concentrations were below 24 g/L (Waldner and Rosengren, 2009). Although in the present study, serum IgG concentrations and failed transfer of passive immunity were not significantly different by medication group, serum IgG concentration was an important factor that influenced ADG to 7 to 10 d of age. Other studies have shown that lower IgG concentrations were associated with higher morbidity, mortality, and lower ADG in beef calves (Dewell et al., 2006). Our lack of significant difference between medication groups on passive immunity may have been due to on-farm protocols to intervene with colostrum consumption by 1 to 4 h after birth, as is currently recommended to decrease the risk of failed transfer of passive immunity and associated health issues (Godden, 2008).

The risk of acidemia and hypoxia is higher in assisted calves, which can lead to increased risk of stillbirth or decreased vigor in newborn calves (Breazile et al., 1988; Vaala and House, 2002). Blood gas disturbances, lower packed cell volumes, and elevated blood L-lactate concentrations are associated with severe acidemia and hypoxia at birth (Homerosky et al., 2017a). Other outcomes associated with acidemia and hypoxia at birth include taking longer to stand, increased risk of failed transfer of passive immunity, and preweaning morbidity and mortality (Szenci et al., 1988; Boyd, 1989; Besser et al., 1990; Schuijt and Taverne, 1994). Vigor assessments can include reflexes such as tongue withdrawal and suckle reflex, as well as time to stand and nurse (Barrier et al., 2012a; Murray et al., 2016b; Homerosky et al., 2017a,b). In this study, the vigor assessments indicated that some calves were less vigorous at birth than other calves. Although it was not possible to investigate the impact of meloxicam on the clinical assessment of vigor in the present study, there was no significant difference between calves that received meloxicam versus a placebo in their odds of standing or nursing within 1 h. Behaviors such as time to stand and nurse were expected to be impacted by treatment of meloxicam-medicated calves because changes in behaviors associated with pain and distress are decreased in calves treated with meloxicam after painful stimuli such as dehorning, castration,

or a difficult birth (Heinrich et al, 2010; Murray et al., 2016b; Olson et al., 2016). However, it was not the case in this study.

Factors such as weakness, trauma, and subsequently failed transfer of passive immunity can lead to increased risk of morbidity and mortality in the preweaning period (Bellows et al., 1987; Wittum and Perino, 1995; Vaala and House, 2002). Specifically, a difficult birth increases the risk of stillbirth and mortality in the first 30 d of life, and increases the odds of bovine respiratory disease and preweaning calf diarrhea (Nix et al., 1998; Lombard et al., 2007). In the current study, there was no association between being medicated with meloxicam or a placebo at birth and treatment and mortality outcomes. This could be because the sample size was not sufficient to measure this difference with so few calves that were treated for disease ($n = 5$) or that died ($n = 6$), despite this being a large proportion of calves that were enrolled in the study. There were differences in treatment and mortality risks between the two farms, which had different periparturient management procedures. This could be explained by the findings in other studies that associated high difficult calving rates and calving management practices with high herd-level calf morbidity (Sanderson and Dargatz, 2000). Cow–calf preweaning mortality is about 7% and most preweaning mortality occurs in first 3 d of life, usually due to dystocia (Patterson et al., 1987). Half of the calf deaths in this study were within the first 4 d of life and were associated with complications of a difficult birth. The much higher mortality risk (18%) in the present study population is attributable to the fact that only assisted calvings were enrolled.

Potential weaknesses of this study include sample size, possible non-differential misclassification bias, and high variability between animals. Post hoc sample size calculations for this study indicated a need for a higher number of animals than the *a priori* sample size calculations and suggested the actual sample size was too small to detect a significant difference. Predicting when a heifer or cow will need assistance at birth is difficult and dependent on multiple management variables. These criteria limited the number of assisted calves available to be enrolled in this study. Due to the challenge of consistently and objectively describing dystocia, assistance at birth stratified by calving difficulty was considered the most accurate way of categorizing calvings for this study. This may lead to some misclassification due to subjectivity of the measure and the influence of on-farm protocols to decide when to intervene. However, randomization

of medication group should have minimized the impact of this. Neonatal physiology is quite complex and variable in dystotic calves. Determining when stage 1 or stage 2 labor actually begins is difficult to measure, which may affect the duration of calving prior to the decision to intervene with delivery and can increase the variability in physiological parameters. Other effects of neonatal physiology that impacts calf vigor and viability include hypoxia and acidosis. It is difficult to determine at birth, without further blood analysis, if a calf is less vigorous because of trauma due to a difficult calving, because of hypoxia and acidosis caused by a prolonged calving, or both. It is not expected that an NSAID would improve vigor if the calf was hypoxic or acidemic, which may have impacted the findings of this study.

Although few positive effects of meloxicam were found in this study, no negative effects were detected either. There were no pathological findings consistent with NSAID toxicity upon gross necropsy and histological examination of calves that died. There was no difference between meloxicam- and placebo-treated calves on hepatic and renal biochemical enzymes to indicate a negative effect of meloxicam on neonatal calves. Although there was no difference between medication groups, calving in either group demonstrated biochemical parameters outside the reference range for adult cattle used by the laboratory. There are few references indicating normal biochemical parameters for neonatal calves in the first 24 h of life or any age-related changes (Knowles et al., 2000; Mohri et al., 2006), which indicates a need for further investigation in the physiology of organ function in newborn calves.

Methods described to assess pain in cattle include physiologic changes (serum cortisol, heart rate, feed intake, and ADG), neuroendocrine changes (substance P, infrared thermography, heart rate variability, skin electrical impedance, and electroencephalography), and behavioral changes (visual scoring systems, videography, vocalization, chute behavior, pedometers, and accelerometers) (Coetzee, 2013). Although physiologic and neuroendocrine changes were measured in this study, behavioral pain assessment was not. This was due to on-farm protocols that intervened frequently with the cow–calf pairs throughout the 24-h period. Future studies investigating pain associated with assisted calvings might evaluate behavioral effects as well as other physiologic and neuroendocrine changes to better understand pain associated with assistance at birth.

CONCLUSION

This study demonstrated a potential growth benefit to meloxicam-medicated calves assisted at birth by an increased ADG of 0.3 kg/d in the first 7 to 10 d of life. It did not find other effects of administering meloxicam at birth to assisted calves and there was no decrease in physiological indicators of pain and inflammation, or improvements in passive immunity or health. Future studies are warranted to further investigate how meloxicam affects neonatal pain and inflammation as well as how it is associated with calf health and productivity. Although this was a small study, improvements in early growth suggest meloxicam given to assisted calves at birth may indicate an important management tool for improving production and well-being in assisted calves.

Conflict of interest statement. None declared.

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