



A randomised controlled trial investigating the effects of administering a non-steroidal anti-inflammatory drug to beef calves assisted at birth and risk factors associated with passive immunity, health, and growth

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ABSTRACT

Background The objectives of this study were to investigate the impact of pain mitigation at birth to assisted beef calves and determine the risk factors associated with transfer of passive immunity (TPI), health, and growth.

Methods Two hundred and thirty cow–calf pairs requiring calving assistance were enrolled. Calves were randomised to receive meloxicam (0.5 mg/kg) or an equivalent volume of placebo subcutaneously at birth. Calf blood samples were collected between one and seven days of age to determine serum immunoglobulin (IgG) concentration. Colostrum intake, treatment for disease, mortality, and weaning weights were recorded. Multilevel linear or logistic regression models were used to determine the effects of meloxicam and to identify risk factors.

Results There was no effect of meloxicam on serum IgG concentrations, average daily gain (ADG), or risk of inadequate TPI (serum IgG concentration <24 g/l), treatment for disease, or mortality ($P>0.05$). Bottle or tube feeding calves were associated with decreased serum IgG concentrations ($P=0.01$) compared with nursing. Calves with an incomplete tongue withdrawal reflex had higher odds of being treated for disease compared with those with complete withdrawal ($P=0.009$). Being born meconium-stained and having decreased serum IgG concentrations were associated with an increased risk of mortality ($P=0.03$). Being born of a mature cow, having a higher birth weight, and increased serum IgG concentrations were associated with greater ADG to weaning ($P<0.05$).

Conclusion Vigour assessment at birth along with good colostrum management may be important to improve TPI and health in high-risk calves such as those assisted at birth.

INTRODUCTION

Growing consumer interest in food production puts pressure on the beef industry to

ensure practices are sustainable and welfare-friendly.^{1,2} In particular, the pain and suffering of animals are considered major concerns for the public and producers.^{3–5} Therefore, providing producers with practical knowledge and on-farm strategies to improve cattle health and welfare is important for the economic sustainability of the beef industry and the Canadian economy.

Calf health and survival are major concerns of cow–calf producers.⁶ Calves assisted at birth are often compromised and experience acidaemia, hypoxia, and soft tissue damage.^{7,8} A compromised calf may be delayed in consuming colostrum and have an increased risk of inadequate transfer of passive immunity (TPI),^{8,9} raising their odds of preweaning morbidity, mortality, and reduced growth.^{10–12} Specifically, a difficult birth increases the risk of mortality in the first 24 hours of life (stillbirth) and in the first 30 days of life, and increases the odds of bovine respiratory disease (BRD) and preweaning calf diarrhoea (PCD) in early life.^{13,14}

Although the incidence of calving assistance is low in western Canada, ranging from 5 per cent to 9 per cent,^{15,16} the majority of producers assist one or more calving each year. This means that managing compromised calves is still a required task for most cow–calf producers. Investigating risk factors associated with TPI, health, and growth is important to identify areas where management techniques could be implemented to improve calf health and welfare. Understanding the

effects of an assisted calving will guide interventions for compromised calves after a difficult birth, including but not limited to the development of pain mitigation strategies for newborn calves.

In cattle, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used form of pain control.⁵ The NSAID class of drugs acts by inhibiting cyclooxygenase isoenzymes (COX1 and COX2) to prevent the inflammatory cascade and reduces prostaglandin synthesis.¹⁷ This provides multimodal relief through analgesic, anti-inflammatory, antipyretic, and antiendotoxic properties.¹⁸ Meloxicam is a COX2 preferential inhibitor NSAID, so it causes fewer negative side effects and has high bioavailability with a prolonged half-life in comparison with other NSAIDs.¹⁸ A few studies have shown positive effects of administering an NSAID at birth to dairy and beef calves,^{19–21} but a large-scale field trial that accounts for confounding risk factors and ranch management is needed.

The objectives of this study were to investigate the impact of administering meloxicam at birth to calves born with assistance and to investigate the risk factors associated with TPI, health, and growth in preweaned beef calves. The hypothesis was that the use of meloxicam would decrease the pain and inflammation associated with an assisted birth and lead to improved TPI, decreased risk of morbidity and mortality, and increased growth in the preweaning period.

MATERIALS AND METHODS

A proposed sample size was calculated based on the likelihood of producers to intervene with colostrum administration in assisted beef calves. Based on previous research by this group showing 45 per cent of calves assisted at birth required intervention to ensure colostrum consumption,²² and using a confidence level of 95 per cent and a power of 80 per cent, a sample size of 200 assisted calves was deemed necessary. Fifteen ranches located in southern Alberta were recruited through two veterinary practices to participate in the study. Ranches were selected based on willingness to participate, good record-keeping, and close proximity to the University of Calgary. To allow for attrition, 230 cow–calf pairs requiring assistance at calving were enrolled from January to June 2017.

Individual cow–calf pair information recorded at birth included date and time of calving, dam parity (heifer or mature cow), dam body condition score (BCS), calf birth weight, sex, breed, calving difficulty, presentation (anterior or posterior), and meconium staining (present or absent). Producers were trained to assign a BCS on the scale of 1 through 5 to dams at calving.²³ Calf birth weight was either estimated using a foot weight tape (Calfscale, Ames, Iowa) or determined using a digital scale. Calving difficulty was defined as the following: easy, one person manually pulling to deliver the calf; and difficult, two or more people pulling to deliver the calf, or mechanical extraction (ie, calf jack) or caesarean section (c-section).

Within 10 minutes after birth, calf vigour was assessed using the vigour parameters described by Homerosky and others^{7,22} that were associated with acidaemia and likelihood of nursing by four hours after birth. These parameters included mucous membrane colour, tongue withdrawal and suckle reflex. Mucous membrane colour (pink or abnormal) was measured by the colour of oral mucous membranes. Tongue withdrawal (complete or incomplete) was measured by pulling the tongue from the calf's mouth and determining if it withdrew the tongue back into its mouth. Suckle reflex (strong or weak) was measured by placing a finger in the calf's mouth and feeling if it suckled the finger.

Calves were randomised to a medication group using a computer-assisted randomisation chart (Microsoft Excel, Microsoft Corporation, Redmond, Washington) stratified by calving difficulty on each ranch. At birth, calves received a subcutaneous dose of meloxicam (Metacam, 20 mg/ml, 0.5 mg/kg, Boehringer Ingelheim, Ingelheim, Germany) or an equivalent volume of placebo (0.025 ml/kg sterile saline with 1 per cent vitamin injectable solution (Vitmaster NF, Vetoquinol, Lavaltrie, Quebec, Canada) to match the colour of meloxicam). Ranch personnel were blinded to the medication group. If ranch personnel were uncomfortable with an assisted calf being enrolled in the study and potentially not receiving pain mitigation, it was not enrolled.

Ranch personnel recorded the approximate time to stand within four categories (ie, 0–30 minutes, 30–60 minutes, 1–6 hours or required assistance) and the time to colostrum consumption within five categories (ie, <1 hour, 1–2 hours, 2–3 hours, 3–4 hours or ≥4 hours). The method of colostrum consumption (ie, nursed from dam, bottle-fed, or tube-fed) as well as the type of colostrum (ie, dam colostrum or colostrum replacement product) were recorded. Bottle-fed and tube-fed methods of colostrum consumption were later combined into one category because some producers attempted to bottle-feed calves first but, when unsuccessful, would then tube-feed calves.

Research personnel visited the ranches after being notified of an enrolled calf to collect blood samples from calves between one and seven days of age. Blood samples were collected from the jugular vein using a vacutainer needle (20 G x 1 inch; Airtite Product, Virginia Beach, Virginia) into a 6-ml coagulating tube (BD Vacutainer, BD, Franklin Lakes, New Jersey). The blood samples were placed on ice in a cooler during transport. They were then centrifuged for 20 minutes at 3000 x g (LWS M24 Combo Centrifuge, LW Scientific, Lawrenceville, Georgia). Serum was removed from the blood collection tubes, placed in 2-ml cryotubes and immediately frozen at –18°C. Once per week, samples were transferred to a –80°C freezer until further analysis. Serum samples were analysed using an in-house radial immunodiffusion assay at the Saskatoon Colostrum Company Quality Assurance Laboratory (Saskatoon, Saskatchewan) as described by Chelack and others.²⁴

Data recorded by ranch personnel included treatment for disease (eg, BRD or PCD), mortality, and when possible, weaning weights. Calves that were enrolled and died before six weeks of age were submitted for post-mortem examination at the University of Calgary Faculty of Veterinary Medicine's Diagnostic Services Unit to determine the cause of death and investigate any potential negative effects, such as lesions in the abomasum, colon, or kidneys, of administering an NSAID at birth.

To describe calving and colostrum management techniques of the enrolled ranches, a survey was conducted at the end of calving season at each ranch. Questions included peripartum management and protocols for calving and postnatal procedures.

Data were analysed with Stata V.14.1 software (StataCorp LP, College Station, Texas). Descriptive statistics and tests for normality were assessed on all continuous variables before model building. Calves with missing medication group data (n=5) were removed from the data set for all analyses. Additionally, calves born via c-section (n=4) and calves from two farms with only one calf enrolled each (n=2) were removed from the data set for regression analysis. Multilevel linear regression models with ranch as a random effect were generated for the outcomes of serum IgG concentration and average daily gain (ADG) to weaning. Multilevel logistic regression models with ranch as a random effect were generated for inadequate TPI (serum IgG concentration <24g/l), treatment for disease and mortality. Potentially significant covariates (ie, dam parity and BCS, calving difficulty, calf sex, presentation, meconium staining, vigour assessment, birth weight, time to stand and nurse, and method or type of colostrum consumed) were offered to the models. Serum IgG concentration was offered as a covariate to the treatment for disease, mortality, and ADG models. Univariable analysis was performed on all covariates using $P \leq 0.15$ as the inclusion criterion for the models.²⁵ Multicollinearity was assessed using Spearman's rank correlation and parameters with a coefficient ≥ 0.7 were considered to be collinear. If collinearity occurred between variables, two different models were built including each variable and assessed using the lower Akaike Information Criterion number to determine the best model. All models were analysed using backwards stepwise regression model-building strategies and non-significant terms were removed except the medication group, which was forced into the model because it was the variable of interest.²⁵ The significance level to be retained in the model was $P \leq 0.05$. Partial F-tests were used to assess the effect of removing categorical variables from the models. Linear models were checked for assumptions by Cook-Weisberg test for heteroscedasticity and Shapiro-Wilk W test for normality. Residual-versus-fitted plots were assessed visually. Individuals that were outliers or leveraged the data were assessed using Cook's Distance and the studentised DFIT command and removed. The proportion of variance

for continuous outcomes was calculated (equation 1) and reported as percentages.²⁶

Equation 1:

$$\frac{(\sigma_{\text{ranch-level effect OR } \sigma_{\text{individual effect}})^2}{(\sigma_{\text{ranch-level effect}})^2 + (\sigma_{\text{individual effect}})^2}$$

The proportion of variance for categorical outcomes was calculated (equation 2) and reported as percentages.²⁶

Equation 2:

$$\frac{(\sigma_{\text{ranch-level effect}})^2}{(\pi^2/3) + (\sigma_{\text{ranch-level effect}})^2}$$

RESULTS

A survey was performed to describe the calving management on each ranch. One ranch did not calve heifers during the 2017 calving season. All 15 ranches assisted calvings as necessary, and the majority would intervene no later than 90 minutes after the feet or an amniotic sac were observed (heifers: 71 per cent; cows: 47 per cent) or no progression was identified (heifers: 93 per cent; cows: 80 per cent) in a calving dam. Detailed information about the timing of calving intervention is described in [table 1](#). Of the 15 ranches enrolled, all used some methods to determine if a calf had received colostrum (ie, saw the calf suck from the dam, the cow's udder appeared less full, the calf appeared full). Various methods to ensure a calf consumed colostrum if it had not been observed to have nursed from the dam were used: all ranches would attempt to place the cow and calf together to encourage nursing, 11 of 15 ranches would restrain the cow in a chute and allow the calf to nurse, and 10 and 12 out of 15 ranches would bottle-feed or tube-feed the calves, respectively.

Of the calves enrolled, 114 received placebo and 111 received meloxicam. Overall, the mean dam BCS was 3.6 out of 5 (sd=0.9), with a mean of 3.6 (sd=0.85) for placebo-treated calves' dams and a mean of 3.5 (sd=0.95) for meloxicam-treated calves' dams. The majority of dams enrolled were heifers (68.9 per cent) and the majority of calves enrolled were bull calves (66.1 per cent) ([table 2](#)). The mean birth weight of calves enrolled was 44.3 kg (sd=6.6), with a mean birth weight of 44.7 (sd=6.8) for placebo-treated calves and a mean birth weight of 43.8 (sd=6.6) for meloxicam-treated calves. Detailed descriptions of the demographics of calves and their dams enrolled by medication group are in [table 2](#).

The majority of calves enrolled had a complete tongue withdrawal reflex (73 per cent), strong suckle reflex (56 per cent) and normal mucous membrane colour (64 per cent) when assessed at birth. Detailed descriptions of vigour assessment, time to stand, and colostrum management by medication group are in [table 3](#). An equal number of placebo-treated (n=96) and meloxicam-treated (n=96)

Table 1 Calving management strategies on 15 cow–calf ranches located in southern Alberta during the 2017 calving season

Management practice	Number of Ranches	
	Heifers (n=14)*	Cows (n=15)
Frequency of checking dams during daylight hours		
Every 1–2 hours	7	4
3–6 times a day	5	9
Twice a day	2	2
Frequency of checking dams during night hours		
Every 1–2 hours	5	2
3–6 times at night	3	4
Twice at night	5	6
Do not check dams at night	1	3
Time to intervene after dam water bag or feet showed (minutes)		
30–60	4	4
60–90	6	3
90–120	1	2
>120	3	6
Time to intervene after dam is not showing progression with labour (minutes)		
30–60	11	9
60–90	2	3
90–120	0	1
>120	1	2

*One ranch did not calve heifers during the 2017 calving season.

calves had blood samples taken to measure serum IgG concentrations. The mean serum IgG concentration for all calves was 35.2 g/l (sd=17.1), with a mean of 33.2 g/l (sd=17.8) and 37.2 (sd=16.4) for placebo-treated and meloxicam-treated calves, respectively. Forty-nine calves had inadequate TPI (34.8 per cent), with 28 being placebo-treated calves and 21 being meloxicam-treated calves.

Overall, 23 calves (10 per cent) were treated for disease, with 11 being placebo-treated calves and 12 being meloxicam-treated calves. Twenty-two calves (9.5 per cent) died in the study, with 11 placebo-treated calves (dystocia=1, weak calf syndrome=1, meconium aspiration=1, septicaemia=1, abomasal ulcer=1, BRD=1, PCD=1, unknown=3) and 11 meloxicam-treated calves (dystocia=1, congenital defects=1, lumbar and femoral fractures=1, septicaemia=2, unknown=6). Seventy-five calves treated with a placebo and 74 calves treated with meloxicam had weaning weights recorded. The mean ADG to weaning for placebo-treated and meloxicam-treated calves was 1.04 kg/day (sd=0.21) and 1.05 kg/day (sd=0.02), respectively.

There was no significant effect of administering meloxicam to assisted calves on serum IgG concentration,

risk of inadequate TPI, treatment for disease, mortality, or ADG. Tables 4 and 5 describe the results for the models including the significant covariates.

When evaluating calf-level risk factors associated with the measured outcomes, calves that were bottle-fed or tube-fed had lower serum IgG concentrations than those that nursed from their dam (table 4). Calves with a weak suckle reflex had lower odds of inadequate TPI than those with a strong suckle reflex (table 5). Calves with an incomplete tongue withdrawal reflex had higher odds of being treated for disease in the preweaning period than those with a complete tongue withdrawal reflex (table 5). Calves that were born with meconium staining and had lower serum IgG concentrations had higher odds of preweaning mortality than those that were not meconium-stained at birth or had higher concentrations of serum IgG (table 5). Calves that were born to a mature cow, had higher birth weights, and higher serum IgG concentrations had greater ADG to weaning (table 4). The proportion of variance between ranches and individuals was calculated for each outcome and reported in tables 4 and 5.

DISCUSSION

Non-steroidal anti-inflammatory drugs are increasingly being used in production animals and can improve cattle welfare. Murray and colleagues⁶ found 13 per cent of producers reported using pain mitigation after a difficult birth, while Moggy and colleagues⁵ found 28 per cent of producers used an NSAID in the calf after a difficult birth. More recently, 45 per cent of surveyed western Canadian beef producers (n=97) reported using NSAIDs after a difficult birth in the calf.¹⁶ Although more producers are using pain mitigation after a difficult birth, the effects of administering analgesics have not been thoroughly studied. Studies investigating physiological impacts of administering an NSAID to calves at birth have not shown an effect. Pearson and others²¹ found no significant effect on physiological indicators of pain and inflammation in meloxicam-treated calves in comparison with placebo-treated calves. Similarly, Gladden and others²⁷ found no significant effect of administering ketoprofen to dairy calves within three hours of parturition on cortisol, creatine kinase, plasma L-lactate, or total protein concentration measured 24 hours, 48 hours, or seven days after birth. In contrast, economically relevant factors such as increased growth or feed intake have been demonstrated in NSAID-treated neonatal calves.^{19 21 28} Specifically, Murray and colleagues¹⁹ found that calves treated with meloxicam at birth had greater milk intake compared with calves treated with a placebo, and Pearson and colleagues²¹ found that assisted calves administered meloxicam at birth had greater ADG within the first week of life compared with placebo-treated calves. Although no significant effect on TPI and calf health was found in the present study, other measurements may be used to

Table 2 Demographics of 225 beef calves by medication group

Demographics	Placebo (n=114)		Meloxicam (n=111)		Total (n=225)	
	Count	Percentage	Count	Percentage	Count	Percentage
Parity of dam						
Heifer	74	66.7	77	71.3	151	68.9
Cow	37	33.3	31	28.7	68	31.1
Sex of calf						
Heifer	42	36.8	33	30.8	75	33.9
Bull	72	63.2	74	69.2	146	66.1
Twin						
No	108	97.3	105	97.2	213	97.3
Yes	3	2.7	3	2.8	6	2.7
Calving difficulty						
Easy assist	50	44.6	58	54.2	108	49.3
Difficult assist	59	52.7	48	44.9	107	48.9
Caesarean section	3	2.7	1	0.9	4	1.8
Presentation of calf						
Anterior	92	90.2	91	88.3	183	89.3
Posterior	10	9.8	12	11.7	22	10.7
Meconium staining						
No	81	84.4	81	84.4	96	50.0
Yes	15	15.6	15	15.6	96	50.0

Calves were administered a dose of either subcutaneous meloxicam (Metacam, 20mg/ml, 0.5mg/kg bodyweight, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025ml/kg) at birth. All parameters are presented as counts and percentages.

investigate pain and inflammation in neonates, such as behavioural indicators.

Behavioural indicators of pain and inflammation are important tools for assessing pain.²⁹ Murray and others¹⁹ found calves that received meloxicam at less than six hours of age had greater improvements in vigour from birth to one day of age than those receiving a placebo. Gladden and colleagues²⁰ randomised calves by calving assistance (unassisted or assisted) to receive ketoprofen or placebo treatment within three hours of parturition and found that calves receiving ketoprofen had increased play behaviour and spent less time in lateral recumbency than those receiving a placebo. Although behavioural indicators of pain and inflammation were not measured in this study, these previous studies indicate that administering an NSAID at birth to calves may improve calf welfare.

Vigour assessment has been used to predict outcomes of neonatal vitality in many different species^{30–33} and is associated with acidaemia, trauma, and assistance at calving.^{7 8 34 35} Poor vigour can have negative outcomes for a calf, such as resulting in taking longer to stand and inadequate intake or timely consumption of colostrum.^{22 36 37} In this study, vigour was an important predictor of TPI and calf health. Specifically, calves with a weak suckle reflex had lower odds of inadequate TPI than those with a strong suckle reflex. In contrast

to the findings of the present study, previous work conducted by the authors' research group has shown that calves with a weak suckle reflex were less likely to nurse from their dam by four hours after birth²² and had lower concentrations of serum IgG⁸ compared with those with a strong suckle reflex. Producers involved in the present study were aware of the associations between suckle reflex and colostrum consumption, and it is speculated that this knowledge influenced their colostrum intervention strategies and they may have managed these calves differently.

In this study, calves with an incomplete tongue withdrawal reflex had higher odds of being treated for disease in the preweaning period than those with a complete tongue withdrawal reflex. This may be due to the relationship between acidaemia and inadequate TPI in less vigorous calves.^{38 39} Specifically, an incomplete tongue withdrawal reflex is associated with neonatal acidaemia and inadequate TPI,^{7 8} and acidaemia has been associated with increased risk of inadequate TPI.³⁸ Acidaemia and inadequate TPI are associated with higher morbidity in preweaned calves^{10 12 40 41}; therefore, this may explain the relationship found between an incomplete tongue withdrawal and increased risk of treatment for disease.

Calves that were born to a mature cow, had higher birth weights, and higher serum IgG concentrations had greater ADG to weaning. Higher serum IgG concentrations have

Table 3 Vigour assessment and colostrum management for 225 beef calves by medication group

Variable	Placebo (n=114)		Meloxicam (n=111)		Total (n=225)	
	Count	Percentage	Count	Percentage	Count	Percentage
Tongue pinch withdrawal						
Complete	76	71.0	78	75.7	154	73.3
Incomplete	31	29.0	25	24.3	56	26.7
Suckle reflex						
Strong	59	57.3	56	55.4	115	56.4
Weak	44	42.7	45	44.6	89	43.6
Mucous membrane colour						
Normal	70	65.4	64	62.1	134	63.8
Abnormal	37	34.6	39	37.9	76	36.2
Time to stand						
0–30 minutes	20	22.7	20	24.1	40	23.5
30–60 minutes	36	40.9	27	32.6	63	36.8
1–6 hours	28	31.8	30	36.1	58	33.9
Required assistance	4	4.6	6	7.2	10	5.8
Method of colostrum consumption						
Nursed from dam	79	78.2	73	78.5	152	78.4
Bottle-fed or tube-fed	22	21.8	20	21.5	42	21.6
Type of colostrum consumed						
Dam's colostrum	88	83.8	82	86.3	170	85.0
Replacer product	17	16.2	13	13.7	30	15.0
Calf nursed from the dam						
Yes	80	83.3	79	88.8	159	86.4
No	15	16.7	10	11.2	25	13.6
Time to consume colostrum (hours)						
<1	20	19.8	19	19.6	39	19.7
1–2	22	21.8	21	21.6	43	21.7
2–3	27	26.7	28	28.9	55	27.8
3–4	19	18.8	22	22.7	41	20.7
4+	13	12.9	7	7.2	20	10.1

Calves were administered a dose of either subcutaneous meloxicam (Metacam, 20mg/ml, 0.5mg/kg bodyweight, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025ml/kg) at birth. All variables are presented as counts and percentages.

been associated with greater ADG to weaning.¹² Older dams produce higher immunoglobulin concentrations in colostrum^{9 42 43} and greater volumes of colostrum and milk,⁴⁴ which may explain why older parity dams weaned calves with better growth.

Colostrum management is an important tool to help improve TPI in high-risk calves.⁴⁵ In this study, the method of colostrum consumption (nursed from dam) was associated with higher serum IgG concentrations than calves that were bottle-fed or tube-fed colostrum. In contrast, Filteau and others⁴⁶ found beef calves who were bottle-fed had a lower risk of failed TPI than those who were left with their dam or led to the udder. This may be due to different management techniques and housing of animals in that study, where cow–calf pairs

housed in stanchion barns were at higher risk of failed TPI. In the current study, all ranches calved outside in small paddocks or larger pastures.

The relationship between calves nursing from dams and having higher serum IgG concentrations may be due to a difference in colostrum quality, which was not evaluated in this study, rather than the method of colostrum consumption per se. Priestley and others⁴⁷ found that calves that received maternal colostrum had higher serum total protein and serum IgG concentrations and were more likely to have adequate TPI compared with those fed plasma or colostrum-derived colostrum replacement products. Calves fed maternal colostrum also had higher weaning weights and ADG, and lower morbidity and mortality. Maternal colostrum is generally considered to

Table 4 Multilevel linear regression models of serum IgG concentrations and average daily gain to weaning in 219 beef calves assisted at birth and medicated with subcutaneous meloxicam (Metacam, 20 mg/ml, 0.5 mg/kg bodyweight, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 ml/kg) while adjusting for covariates and clustering by ranch

	Coefficient	se	P value	Proportion of variance (%)	
				Individual level	Ranch level
Serum IgG concentration, g/l				>99	<1
Medication group					
Placebo	Referent	–			
Meloxicam	3.6	2.6	0.2		
Method of colostrum consumption					
Nursed from cow	Referent	–			
Bottle-fed or tube-fed	–8.5	3.2	0.008		
Average daily gain to weaning, kg/day				96.8	3.2
Medication group					
Placebo	Referent	–			
Meloxicam	0.02	0.03	0.4		
Dam parity					
Mature cow	Referent	–			
Heifer	–0.1	0.04	0.02		
Birth weight, kg	0.009	0.002	<0.0005		
Serum IgG concentration, g/l	0.002	0.0008	0.008		

be superior to a replacement product, but if the maternal colostrum quality is poor (eg, low IgG concentration, high bacterial count, possible transmission of diseases, low volume) then a replacement product may be the better option.⁴⁵ Therefore, the type and quality of colostrum may have more of an effect than the method of consumption. In the current study, calves that nursed from their dam always received maternal colostrum, but those that were bottle-fed or tube-fed may have received colostrum replacement product or maternal colostrum. The type and method of colostrum administration had high collinearity and therefore were not offered to the model simultaneously.

Being born with meconium staining and having lower serum IgG concentrations increased the odds of preweaning mortality in assisted calves in this study. This is consistent with other studies where higher serum IgG concentrations were associated with a lower risk of mortality.^{9,12} Ranch personnel involved in this study always checked to make sure a calf consumed colostrum, and if the calf had not, they intervened with various colostrum management techniques, which may explain high serum IgG concentrations in this population. Similar colostrum management practices have been reported on western Canadian cow–calf operations.^{6,16}

Meconium staining occurs when the fetus experiences intrauterine hypoxia and meconium is expelled into the amniotic sac causing a yellowish-brown staining of the skin and hair. Aspiration and inhalation of meconium can lead to partial airway obstruction, ventilation-perfusion mismatch, chemical pneumonitis, and disruption of surfactant function.⁴⁸ Hypoxia and meconium aspiration have both been

associated with a higher risk of mortality in multiple neonatal species, including human beings, piglets, and calves.^{49,50}

The majority of the proportion of variance accounted for in these models was at the individual level rather than the ranch level. These findings indicate that ranch-level factors had minimal impact on the outcomes and that most of the variance in the models was at the individual calf level. For treatment for disease, half of the variance was due to ranch-level influences, which may be explained by differences in treatment intervention protocols by ranch.

A potential bias of this study was that producers had the option to not enrol difficult assisted calves. Because all the ranches enrolled were working cow–calf operations, producers were allowed to not enrol a calf if they were uncomfortable with the possibility that a calf might receive a placebo, as many already had pain mitigation strategies in place. Although the number of calves on each ranch that were not enrolled in the study is unknown, this may have biased the sampled population to calves that had less traumatic deliveries or were apparently less compromised at birth. An effect of meloxicam on calf health may not have been seen due to this selection bias. Another potential bias was that ranches selected to be enrolled in this study were well-managed ranches, intervening with calving assistance early and administering colostrum to calves that were not observed to consume colostrum on their own, which may have lessened the impacts of a difficult calving on calf health and growth.

Although a few studies have investigated the effects of administering an NSAID to neonatal calves, none has reported pathological side effects.^{19–21,27,28} Several studies



Table 5 Multilevel logistic regression models of transfer of passive immunity, treatment for disease, and mortality in calves assisted at birth and medicated with subcutaneous meloxicam (Metacam, 20 mg/ml, 0.5 mg/kg bodyweight, Boehringer Ingelheim, Ingelheim, Germany) or placebo (0.025 ml/kg) while adjusting for covariates and clustering by ranch

	Odds ratio	se	P value	Proportion of variance	
				Individual level	Ranch level
Inadequate transfer of passive immunity (<24 g/l IgG)				>99	<1
Medication group					
Placebo	Referent	–			
Meloxicam	0.6	0.2	0.2		
Suckle reflex					
Strong	Referent	–			
Weak	0.5	0.2	0.05		
Treatment for disease					
				46	54
Medication group					
Placebo	Referent	–			
Meloxicam	1.7	1.0	0.4		
Tongue withdrawal reflex					
Complete	Referent	–			
Incomplete	5.8	3.9	0.009		
Mortality					
				97.6	2.4
Medication group					
Placebo	Referent	–			
Meloxicam	2.0	1.4	0.3		
Meconium staining					
No	Referent	–			
Yes	5.4	3.8	0.02		
Serum IgG concentration, g/l	0.95	0.02	0.03		

have investigated the negative side effects of NSAIDs in neonatal foals, indicating repeated and higher doses of flunixin meglumine associated with stomach ulcerations and petechiations of the caecum and colon,⁵¹ but no side effects were found with daily administration of meloxicam in foals two to three days old.⁵² Drug clearance has also been demonstrated to be different in neonatal foals in comparison with adult horses.^{53 54} However, these studies were performed in healthy foals, and NSAIDs in neonates that are dehydrated, have poor tissue perfusion, or are hypovolaemic may be at greater risk of negative side effects and require further investigation.

CONCLUSIONS

This study identified several factors that can be identified at birth that were associated with an increased risk of inadequate TPI, treatment for disease, mortality, and reduced growth. Although there was no effect of giving an NSAID at birth to assisted calves on TPI, health, and growth, assessing vigour at birth and ensuring good colostrum management may be important to improve TPI and health in high-risk calves such as those that are assisted at birth.

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