The effects of pretransportation or arrival meloxicam administration to calves entering the feedlot on morbidity, biomarkers, performance, and carcass characteristics

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ABSTRACT: The objective of this trial was to investigate the effects of using meloxicam as a pretransport or on arrival therapeutic on disease outcomes of bovine respiratory disease (BRD), biomarker outcomes associated with BRD, performance characteristics over the first 42 d on feed, and carcass traits at harvest in cross bred beef cattle. Multisourced, crossbred steer calves (n = 168) consisting of mainly British and British-Continental breeds were purchased from an auction market in central Missouri. Calves were processed prior to transportation and again upon feedlot arrival. Animals were randomized to 3 separate treatments: pretransport meloxicam (PMEL), arrival meloxicam (AMEL), and a control group receiving inactive excipient (CONT). Dosing at 1 mg/kg on weighted averaged administered per os. Animals were weighed and blood was collected pre- and post-transport. Haptoglobin (Hp)-matrix metaloproteinase (MMP)-9 complex, cortisol, and substance P were quantified. Weights were taken again at 42 d and at harvest. Clinical signs of BRD were monitored using indicators of depression, appetite, respiration, and temperature that qualified the animals for treatment. Harvest parameters were collected using a standardized United States Department of Agriculture grading system for quality grade and yield grade. Meloxicam did not have a significant effect on BRD morbidity over the course of the study and there was no significant effect on performance characteristics at 42 d ($P > 0.10$). Of the calves that did succumb to BRD, no significant differences were found in severity of disease ($P > 0.10$). Concentrations of substance P and Hp-MMP-9, were increased on arrival ($P \leq 0.05$) however no significant treatment effect or interaction were found between AMEL, PMEL, CONT, or across different levels of biomarkers ($P > 0.10$). Meloxicam use prior to or on arrival does not mitigate disease or improve performance during the feeding period.

Key words: bovine respiratory disease, biomarkers, cattle, meloxicam, performance

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INTRODUCTION

Lighter body weight cattle, that are transported long distances, are at a greater risk of morbidity and subsequent mortality due to bovine respiratory disease (BRD) (Cernicchiaro et al., 2012). Cattle at high risk for BRD, subjected to stressors such as transportation, have decreased immune function (Caswell, 2014). Physical and psychological stress during transit results in changes of circulating biomarkers that indicate inflammation and disease occurrence modifications of the liver and immune system. Acute phase proteins are considered important markers of transportation stress that are released from the immune system and shifts the liver to an immune organ (Earley and Murray, 2010; Cooke et al., 2013b). Furthermore, connecting these markers to disease and evaluating the effects of therapeutics on these markers could help in future preliminary diagnosis of BRD.

Previous studies have reported reduced lung consolidation when nonsteroidal anti-inflammatory drugs (NSAIDs) were administered as an adjunct to antibiotics (Lockwood et al., 2003). European legislation requiring the reduction of antibiotics has incited research for early intervention with NSAIDs to reduce the use of antibiotics and have reported success (Thesing et al., 2016). Recent study directed at the use of NSAIDs in cattle prior to transportation focused on performance, and physiologic outcomes (Guarnieri Filho et al., 2014; Van Engen et al., 2014; Van Engen et al., 2016). Flunixin meglumine, a labeled antipyretic in cattle, was proven ineffective as a potential drug for increased performance on arrival (Cooke et al., 2013a). No investigation has focused on evaluating the effects of using NSAIDs in high-risk cattle, administered prior to transportation, on disease or performance outcomes past 21 d into the feeding period. We hypothesized that treatment with meloxicam prior to or on arrival after transportation would result in reduction of disease and increased performance in the first 42 d of the feeding period and improved carcass characteristics at harvest. Therefore, the objectives of the present study were to investigate the effects of using meloxicam as a pretransport or on arrival therapeutic on disease of BRD, biomarker outcomes associated with BRD, performance characteristics over the first 42 d on feed, and carcass traits at harvest in cross bred beef cattle.

MATERIALS AND METHODS

Before the initiation of this experiment, all animal use, handling, and sampling techniques described were approved by the Oklahoma State University animal care and use committee (# AG-16-1).

Study Population

Crossbred steer calves (n = 168) consisting of mainly British and British-Continental cross breeds were assembled at a livestock auction in west central Missouri. In 2 separate events 1 wk apart, an order buyer purchased calves deemed to be high risk from the auction market, with initial body weights (BWs) averaging 251 ± 24 kg. Animals were acquired from multiple sources and comingled within the holding facility of the auction barn for an undetermined amount of time. Prior to enrollment calves were visually appraised and deemed free of musculoskeletal abnormality, normal in attitude and normal in respiratory character (lacking increased respiratory effort, cough, open mouth breathing, etc.). During enrollment, duplicate ear tags with individual identification were assigned and placed in both ears. Eighty-nine and 79 calves were loaded on a road transportation semitruck on 11th and 18th August 2016, respectively. Distance traveled from the livestock market to the research feedlot was 533 km (~8 h). After arrival at the feedlot, calves were allowed to rest for at least 12 h and then processed for sample collection.

Study Design

The study consisted of a blinded, pen randomized design with 3 parallel arms. The 3 arms consisted of a pretransportation meloxicam with on arrival placebo (PMEL; n = 62), pretransportation placebo with on arrival meloxicam (AMEL; n = 53), and controls that received placebo both pretransportation and on arrival (CONT; n = 53). Meloxicam (USP; Aurobindo Pharma USA, Dayton, NJ) at 255 mg dosing per os (PO) was calculated based on the estimated weight average of 255 kg to 1 mg/kg of BW. CONT placebo was a sham bolus. Pen assignments were randomized to AMEL, PMEL, and CONT treatments. The calves within the 3 treatments were randomized to pens (n = 18). Numbers of animals were balanced as best as possible based on incoming numbers of animals and pen availability. PMEL, AMEL, and CONT were allotted to an equal number of pens (n = 6).

Initial Processing

During enrollment at the auction market, BW and blood samples were collected. Scales were tared

to zero and verified accurate prior to use using a test weight and individual animals weights were hand recorded. Bolus administration then occurred with appropriate treatments for PMEL, AMEL, and CONT via balling gun. Prior to release each calf was verified to have swallowed the treatment bolus via palpation of the larynx. Cattle were restrained in a processing chute and the head was restrained with a rope halter; blood was acquired via jugular venipuncture into 10 mL vacutainer tubes (Heparin; Becton Dickinson, EDTA; Becton Dickinson and Serum; Becton Dickinson). Initial processing occurred on site in the auction market (day −1). Centrifugation of blood was performed at 3,000 *g* for 15 min at 4 °C. Plasma or serum was immediately collected off the centrifuged vacutainer tube with a micropipette and transferred to micro-centrifuge tubes in duplicate. Samples were then paced on dry ice and transported frozen to the laboratory. Samples were transferred to a freezer and stored at −80 °C.

On Arrival Processing

On arrival at the Oklahoma State Willard Sparks Beef Research Center, cattle were processed within 18 h of arrival. The morning of on arrival processing, all calves received commercially available vaccines against bovine herpes virus-1, BVDV (types 1 and 2), parainfluenza virus 3, bovine respiratory syncytial virus in a 5-way vaccine (Titanium 5; Elanco Animal Health, Greenfield, IN) and clostridal pathogens in a 7-way (Vision 7; Merck Animal Health, Madison, NJ). All calves were administered a growth promoting implant containing 80 mg trenbolone acetate and 16 mg estradiol (Component TE-IS implant; Elanco Animal Health). The antiparasitic protocol required an oral drench (Safeguard; Merck Animal Health) and injectable dewormer (Dectomax; Zoetis Animal Health, Florham Park, NJ). Later in the feeding period, all steers on trial also received a second implant of 4 mg of estradiol and 20 mg of trenbolone acetate (Revalor XS; Merck Animal Health) on day 70.

Blood and BW data were collected as previously described. Calves were then given their second treatment on arrival. Calves in the PMEL and CON treatment groups received an empty placebo bolus. The remaining calves in the AMEL group received meloxicam boluses. Pens were identical in nature and the ration was a total mixed ration that was identical across treatments. Receiving and finishing diets were formulated to meet or exceed national academy of science engineering and medicine requirements of beef cattle nutrition 8 edition (Nutrient Requirement of Beef Cattle, 2014) (Table 1). Steers were housed in open air soil surfaced pens that were 12.2 m × 30.5 m pens, with a 12.2 m × 3.7 m concrete apron, and a 12.2 m concrete fence line bunk with a 76-liter concrete water tank shared between 2 pens. On day 42, calves were weighed to measure performance characteristics. Scales were tared to zero and verified accurate prior to use using a test weight and individual animals weights were hand recorded. Study animals remained in their respective pens throughout the feeding period until their specified harvest date on 7 April 2017.

Assessment of Bovine Respiratory Disease

After receiving training, personnel blinded to treatment were designated to identify cattle with clinical signs of BRD. Steers were evaluated based on the DART system (Depression, Appetite, Respiratory, and Temperature system; Zoetis, Florham Park, NJ) with some modifications (Step et al., 2008; Holland et al., 2011). Assessment occurred once a day in the mornings.

A severity scoring system was used to rank animals that were deemed clinical for BRD. The scale of the score was on a 1 to 4 and was attributed as follows: 1-mild, 2-moderate, 3-severe, and 4-moribund. The scale of the scoring was based off of clinical signs each trained individual was adept at identifying. Specifically, those signs included: animals that were off feed, gaunt in appearance, signs of dyspnea consisting of open mouth breathing with extension of the head and neck, hanging of the head in a depressed manner or a glassy appearance in the eye. Animals assigned a severity score where removed from the pen for further evaluation. Calves with a 1 or 2 severity score were treated if the rectal temperature was 40 °C or greater. Calves with a 3 or 4 severity score were treated regardless of rectal temperature. After treatment, calves were returned to their home pen. A maximum of 3 antibiotic treatments were used per calf before they were deemed a treatment failure. The first treatment consisted of tilmicosin (Micotil; Elanco, Greenfield, IN) at 1.5 mL/45.35 kg BW, the second treatment was florfenicol (Nuflor; Merck, Summit, NJ) at 6.0 mL/45.35 kg BW, and the third treatment was ceftiofur crystalline free acid (Excede; Zoetis, Florham Park, NJ) 1.5 mL/45.35 kg BW for first, second, and third BRD treatments respectively. All antibiotics were administered SQ in the neck with the exception of ceftiofur crystalline free acid being administered SQ into the base of the ear. All dosing instructions were administered as indicated within the product label. Each antibiotic had an observed

Table 1. Composition of common diets

Item†	Receiving	Finishing
Ingredient, %		
Sweet Bran*	54.80	30.00
Prairie hay	30.00	7.00
Dry-rolled corn	10.00	53.50
Dry Supplement B-273‡	5.20	5.50
Dry Supplement B-373¶	—	5.50
Liquid Supplement↓	—	4.00
Nutrient Composition		
NEm, Mcal/kg	1.69	2.23
NEg, Mcal/kg	1.08	1.54
TDN, %	65.90	89.62
CP, %	16.94	15.18
Crude fat, %	2.47	4.40
NDF, %	43.53	23.03
ADF, %	21.18	9.08
Calcium, %	0.63	0.89
Phosphorus, %	0.68	0.55
Magnesium, %	0.32	0.26
Potassium, %	1.25	0.96

ADF = acid detergent fiber; CP = crude protein; NDF = neutral detergent fiber; TDN = total digestible nutrients.

†All values are presented on a DM basis.

*Corn gluten feed product (Cargill, Dalhart, TX)

‡Dry supplement B-273 was formulated to contain (% DM basis) 39.62% ground corn, 29.89% limestone, 20.71% wheat middlings, 6.61% urea, 1.01% magnesium oxide, 0.604% zinc sulfate, 0.38% salt, 0.117% copper sulfate, 0.114% manganese oxide, 0.05% selenium premix (contained 0.6% Se), 0.306% vitamin A (30,000 IU/g), 0.084% (vitamin E (500 IU/g), 0.312% Rumensin 90 (Elanco Animal Health), and 0.192% Tylan 40 (Elanco Animal Health).

¶Dry supplement B-373 was formulated to contain (% DM basis) 39.65% ground corn, 29.57% limestone, 20.49% wheat middlings, 6.74% urea, 1.00% magnesium oxide, 0.598% zinc sulfate, 0.473 Optaflexx (Elanco Animal Health), 0.37% salt, 0.116% copper sulfate, 0.113% manganese oxide, 0.05% selenium premix (contained 0.6% Se), 0.303% vitamin A (30,000 IU/g), 0.082% (vitamin E (500 IU/g), 0.309% Rumensin 90 (Elanco Animal Health), and 0.120% Tylan 40 (Elanco Animal Health).

↓Liquid Supplement was formulated to contain (% DM basis) 45.86% cornsteep, 36.17% cane molasses, 6.00% hydrolyzed vegetable oil, 5.46% 80 VOP/20 oil, 5.19% water, 1.23% urea, 55% solution, and 0.10% xanthan gum (Westway Feed Products, Tomball, TX).

post-treatment interval that required observance prior to any further therapeutic intervention.

Performance and Carcass Characteristics

During the finishing phase, measuring cattle performance, and carcass characteristics were performed in a manner consistent with a previous publication (Holland et al., 2011). The amount of feed per pen was documented on a dry matter basis for the first 42 d and used with day 42 bodyweights to calculate gain to feed. Left over feed or orts was weighed back at the end of 42 d and a dry matter was taken on the orts and subtracted from the total feed. A final bodyweight was captured prior to harvest shipment. Cattle with colored hides other than black were harvested at a commercial processing plant in Dodge City, KS (located at 434 km from the research station). All black hided cattle were harvested in Arkansas City, Kansas (located at 110 km from the research facility). This was done based on contracts for cattle and specific marketing channels the owner of the cattle wished to pursue and was balanced among treatments. Trained Oklahoma State University personnel quantified and recorded carcass characteristics. Data generated in plant included: hot carcass weight (HCW), Ribeye area (REA), marbling score, fat over the 12th rib, yield grade (YG), and quality grade (QG).

Cortisol Analysis

Circulating plasma was analyzed for cortisol and quantified via radioimmunoassay using a commercially available kit at pre and post shipment (Corticote [125 - I] Radioimmunoassay Kit manufacturer: MP Biomedical, Eschwege, Germany).The quantifiable range of the assay was from 2.5 ng to 300 ng/mL. The average standard curve (R^2) was 99.8. Validity of the assays for each run was confirmed with internal standards at 10 and 100 ng/mL. The interassay and intra-assay CV were at < 8% and < 12.5%, respectively.

Substance P Analysis

Substance P concentrations were determined for timepoints from initial processing and on arrival processing. In each 10 mL EDTA blood tube (EDTA; Becton Dickinson), 200 µg benzamidine was added 48 h prior to the start of the study for protease inhibition. Whole blood extracted from the jugular vein was inverted 3 times to guarantee homogenization with the protease inhibitor and EDTA. Substance P levels were determined by radioimmunoassay with previously published methods using nonextracted plasma (Van Engen et al., 2014). The operating range for the assay ranged between 5 and 320 pg/mL. The CV for the intra-assay variability was 9.3% and the interassay variability was calculated to be 18.3%. The average R^2 for the calibration curve was 0.986.

Haptoglobin-Matrix Metalloproteinase-9 Analysis

The Hp-MMP-9 ELISA was performed as described elsewhere (Bannikov et al., 2011; Hinds et al., 2014). The capture antibody was a monoclonal anti-bovine MMP-9 (clone 10.1; native

bovine neutrophil MMP-9 antigen) and wells were blocked by the addition of 300 μL of SuperBlock T20 (Thermo Scientific, Pierce, Rockford, IL). All plates were prepared at the same time to minimize variation between plates.

The serum used as a standard was prepared from an ill bovine sample that had a verified Hp-MMP-9 concentration of 913 ng/mL (Bannikov et al., 2011). This previous aliquoted standard was thawed on ice and sonicated for 3 consecutive 1-min intervals, vortexed, and serially diluted to create a standard curve as follows: 228, 114, 57, 28, 14, 7, and 3.5 ng/mL. Blank wells contained all reagents, with serum from a healthy steer, diluted 1:10 in TBS+Tween 20. Affinity chromatography and Hp-MMP-9 ELISA of this animal's serum demonstrated it was free of demonstrable Hp-MMP-9 (Lakritz J, unpublished observations).

Serum samples from experimental animals were diluted 1:10 with Tris-buffered saline (pH 7.5) to which 0.05% Tween-20 was added (Immunology Consultants Laboratory, Portland, OR, RHPT-10A; 1:5,000 dilution) prior to analysis by ELISA. Diluted standards and serum samples from experimental animals (100 μL) were placed into wells of a 96-well plate in duplicate (16 standards, 40 serum samples/plate) for 2 h on a plate shaker at room temperature. After washing prediluted rabbit-anti-bovine Haptoglobin-HRP conjugate (Kirkegaard & Perry Laboratories, Gaithersburg, MD; 50-76-11), were allowed to bind to haptoglobin that is bound to MMP-9 in the wells on a plate shaker for 1 h. After washing wells 5 times in Tris-buffered saline (pH 7.5) with 0.05% Tween-20, 100 μL of 3,3',5,5'-Tetramethylbenzidine substrate was added/well and color development was allowed for 20 min. After 20 min, 100 μL 0.1 N hydrochloric acid was added/well to stop the enzymatic reaction. Standard and sample absorbance was determined on a micro-plate reader at 450 nM. All samples whose absorbance at 450 nm or greater than the highest standard were rediluted to 1:50 with the Tris-buffered saline (pH 7.5) to which 0.05% Tween-20 was added diluent and reassayed (56 samples total). Sample concentrations were determined by linear regression of the known standard concentration versus absorbance value, using the intercept and slope calculated from the linear regression and corrected for the dilution of the sample (10-fold or 50-fold) (Bannikov et al., 2011). Average coefficient of determination for the calibration curve was 0.996 ± 0.003 and the average coefficient of variation between samples analyzed was 8.4% ± 2.5%.

Statistical Analysis

Statistical analysis was performed using statistical software (SAS 9.4, SAS Institute Inc., Cary, NC). Generalized linear mixed models were fitted to test associations between treatment group with clinical, performance, carcass, and biomarker outcomes. Independent variables consisted of: 1) treatment group (categorical; PMEL, AMEL, and CONT), 2) BW at arrival (categorical; 1 ≤ 233 kg, 2 = 234 to 249 kg, 3 = 250 kg to 266 kg, and 4 ≥ 267 kg), and 3) study day (categorical; −1, 0, 42, and 230 d). Clinical outcomes consisted of: 1) within-pen BRD morbidity (events/trials; calculated as the number of initial BRD cases in each pen divided by the total number of animals in each pen), 2) BRD severity score (ordinal; 0 = normal, 1 = mild, 2 = moderate, 3 = severe, and 4 = moribund), and 3) rectal temperature (continuous). Performance and carcass outcomes included: 1) Average daily gain (ADG) (calculated as final BW – initial BW divided by the number of days), 2) Dry Matter intake (DMI) (kilograms of dry matter fed divided by number of days), 3) BW, 4) HCW, 5) REA, 6) G:F, 7) marbling, 8) dressing percent, 9) yield grade, all continuous, and 10) quality grade (dichotomous; 1 = select and standard, 2 = choice and prime). Biomarker outcomes consisted of: 1) cortisol, 2) substance P, and 3) Hp-MMP-9 complex, which were all transformed using a natural logarithm to meet the normality and homoscedasticity assumptions of the residuals. Models were fitted with a Gaussian distribution and identity link for continuous outcomes, binomial distribution with logit link for event/trials outcomes (BRD), and multinomial distribution, cumulative logit link for polychotomous outcomes. Initial models were fitted using a Laplace likelihood approximation technique in order to quantify overdispersion (Pearson χ^2/df). Final models, when feasible, were fitted using a residual pseudo-likelihood approximation procedure and Newton-Ridging estimation. Akaike and Bayesian Information criteria were used to compare models. We included random intercepts for pen and arrival date in all models. For carcass outcomes, we also fitted a random intercept for harvest site, and for the BW outcome, we included a random intercept for animal in the repeated measures models with an unstructured covariance structure, to account for repeated measures of cattle over time. Models for clinical, performance, and carcass outcomes included fixed effects for treatment group and arrival BW. Models for BW and biomarker outcomes included fixed effects for treatment and

study day and a 2-way interaction between treatment and study day. Model assumptions were tested in all models and residuals were investigated using graphical tools. The Tukey–Kramer multiplicity correction was used for the prevention of multiple treatment group comparison Type I error. Mean values and probabilities and their 95% confidence intervals were computed. Significance was indicated by P values less than or equal to 0.05.

RESULTS

A total of 6 animals were removed from the trial. In the first week of the study, 2 calves developed joint infections. Three months later one study subject died of joint infection. The remaining 3 were removed later in the feeding period due to laminitis, lameness, and respiratory issues. No mortality was evident in the group as a consequence of acute BRD. This is depicted as percent mortality in Table 2 and mortality was not analyzed statistically.

The mean cumulative respiratory morbidity across all trial pens over the entire period was 26.3%. Within-pen morbidity ranged from 0 to 63%. Although not significantly different ($P = 0.87$), mean initial respiratory morbidity (day 1 to 42) as 20.2, 21.0, and 23.1% for PMEL, AMEL, and CONT, respectively. Of note, all pens that experienced 0% morbidity ($n = 3$) were assigned the meloxicam treatment. Further evaluation of first treatment in morbidity over days 1 through 10, and days 1 through 30 are depicted in Table 2. The number of days in the feedlot until the first BRD treatment was needed, relative to day 0, was termed day of treatment. This time to first treatment in days did not differ significantly between treatment groups ($P= 0.71$). In addition, the severity of sickness did not differ ($P = 0.63$) between treatment groups. No significant ($P = 0.79$) differences in rectal temperature between treatment groups were observed in the study calves during clinical evaluation at first treatment.

Evaluation of live performance data occurred over the first 42 d of the trial (Table 3) and again at the final day of the feeding period. Body weights between treatment groups did not differ significantly on individual day comparisons prior to transportation, on arrival or at day 42 of the study period ($P > 0.10$). For all groups, there was no significant difference in weight between day −1 and day 0 ($P > 0.10$). ADG from day 0 to day 42 for AMEL, PMEL, and CONT did not differ statistically between treatment groups ($P = 0.89$). A treatment effect was detected between AMEL and the CONT groups for DMI ($P = 0.01$). DMI was slightly less for AMEL-treated animals compared to controls. DMI depended on BW. As each BW category increased from 1 to 4, there was an increase in the DMI for each group ($P < 0.05$). No differences were seen as an affect of treatment on BW group DMI ($P >0.10$).

Carcass parameters are reported in Table 4. The total number of days on feed was the same for all pens and treatment groups. This was not analyzed statistically and the average for all pens was 235 d on feed. The final BW prior to harvest were similar ($P = 0.63$). There were no differences in ADG over the entire feeding period ($P = 0.42$). HCW did not differ ($P= 0.86$) between treatment groups. BW on arrival at day 0 had significant effect on HCW ($P < 0.05$). Greater HCW was observed in the heaviest weight group (4) in comparison to each of the lower BW categories (1 and 2). In line with the

Table 2. Comparison of orally administered arrival meloxicam (AMEL), or orally administered pretransport meloxicam (PMEL) to control treated steer (CONT) means (±SEM)

Variable, unit	AMEL ($n = 6$ pens)	PMEL ($n = 6$ pens)	CONT ($n = 6$ pens)	SEM	P-value[§]
Total Mortality, %	1.7	3.5	1.1	—	—
Total Morbidity of animals, %[†]	24.5	29.0	25.1	7.01	0.80
First treatment morbidity, %	21.0	20.2	23.1	6.95	0.96
Day 1–10, %	15.1	16.1	17.3	—	—
Day 1–30, %	16.9	20.9	19.2	—	—
Day of treatment[¶]	8.3	10.6	16.4	7.12	0.71
Severity score[‡]	1.8	1.3	1.7	0.42	0.63
Rectal temperature, °C	40.3	40.4	40.6	0.38	0.77

Mean values for total number of animals requiring treatment for BRD, breakdown of the percentages of first treatment and those treated within the first 30 days, severity score, rectal temperature and average day of treatment for BRD, by treatment group.

Significance was defined at $P \leq 0.05$. [†]Total morbidity percent refers to the total number treated per group and includes those animals treated twice within the first 100 days. [¶]Day of treatment refers to the mean day for animals pulled and treated. [‡]Severity score ranged from 1 (mild), 2 (moderate), 3 (severe) to 4 (moribund). — indicates that groups were not analyzed statistically.

Table 3. Comparison of orally administered arrival meloxicam (AMEL), or orally administered pretransport meloxicam (PMEL) to control treated steer (CONT) means (±SEM)

Variable, unit	Time, d	AMEL	PMEL	CONT	SEM	*P*-value*
BW, kg	–1	253.5	252.4	248.4	9.90	0.93
	0	254.8	251.3	245.3	8.61	0.74
	42	330.7	325.2	319.2	10.33	0.74
ADG, kg/d	0–42	1.8	1.8	1.8	0.07	0.89
DMI, kg/d	0–42	7.4[a]	7.5[ab]	7.6[b]	0.05	0.01
Ratio of ADG to DMI, G:F	0–42	0.24	0.23	0.23	0.01	0.80

Mean values of live performance variables at the pen level separated by treatment group.

Treatment administration occurred prior to transport on day −1 and again on day 0 arrival processing. *Significance was defined at $P \leq 0.05$. Superscripts with different letters indicate significance between groups.

absence of treatment differences for the HCW and the final BW outcomes, dressing percentages were not different between groups ($P = 0.59$). Changes in the marbling score ($P = 0.65$) and the measured fat over the 12th rib ($P = 0.58$) were also unaffected by specific treatments at arrival. Ribeye area, YG, and QG of the carcass also remained unchanged ($P > 0.10$). Live and carcass performance were also modeled for the simplified treatment comparison of MEL and CONT. These outcomes are individually displayed in Table 5.

Model-adjusted means for circulating biomarker are presented in Table 6. Cortisol levels in circulating plasma did not differ over time ($P = 0.52$) or by treatment ($P = 0.78$), and there was no interaction ($P = 0.91$) between time and treatment ($P = 0.70$). Substance P concentrations increased over time from day −1 to day 0 ($P < 0.05$), however, they did not differ by treatment group ($P = 0.15$). In circulation, Hp-MMP-9 increased over time ($P < 0.05$), however, there were no differences due to treatment ($P = 0.76$).

Neither treatment groups ($P > 0.75$) nor cortisol concentrations in plasma ($P = 0.90$) were associated with BRD morbidity. Similarly, neither treatment ($P > 0.75$) nor substance P in plasma ($P = 0.20$) were not significantly associated with BRD morbidity. No differences in BRD morbidity was observed across Hp-MMP-9 concentrations in serum ($P = 0.92$) or treatment group ($P > 0.75$).

DISCUSSION

Currently, there is no novel literature that compares the differences of the effect of a NSAID administered prior to transportation or on arrival to mitigate disease or on increased performance. Specifically, no pretransport meloxicam administration studies follow cattle to slaughter to investigate performance compared to negative controls. Drugs with prophylactic and therapeutic effects such as meloxicam can benefit the health of animals by reducing negative effects of pain and stress during transport (Barrier et al., 2014; Van Engen et al., 2014). For cattle, meloxicam has become an intensively investigated extra label drug use NSAID. As described in previous studies, meloxicam offers beneficial effects such as prevention of disease during surgical procedures (Coetzee et al., 2012a) and reduction of pain in common procedures of bovine production medicine (Nagel et al., 2016; Coetzee et al., 2012b). Meloxicam is a member of the oxicam drug class and preferentially inhibits cyclooxygenase II activity, which has a physiologic role in prostaglandin production (Plumb, 2015). Oral administration of meloxicam is pharmacokinetically proven to have high bioavailability and a half-life of 26 h in the ruminating bovine (Coetzee et al., 2015). These properties are advantageous when administering a dose prior to or after transport as well as during other production practices. Recent work indicates that meloxicam dosed prior to transport reduces the stress response associated with transport (Van Engen et al., 2014) and decreases the acute phase protein response while preventing performance losses on arrival (Guarnieri Filho et al., 2014).

With a nonintegrated beef system, economic, geographic, and spatial limitations of feed yard infrastructure results in long distance transportation for most calves (Gorsich et al., 2016). Cattle transport increases likelihood of BRD as well as other factors such as colostrum management at birth (Perino et al., 1995), weaning stress (Marti et al., 2017), and comingling (Arthington et al., 2003). In the present study, we were able to account for and locate calves that were comingled from multiple sources and transported over a long distance. Due to the origination of lightweight calves from an auction market, we suspected that the weaning management was minimal. The environment was ideal for the transmission of respiratory pathogens from infected to naive animals with additional

Table 4. Comparison of orally administered arrival meloxicam (AMEL), or orally administered pretransport meloxicam (PMEL) to control treated steer (CONT) means (±SEM)

	AMEL		PMEL		CONT		
Variable	Mean	(±SEM)	Mean	(±SEM)	Mean	(±SEM)	*P*-value*
Total days in the feedlot	235.0	—	235.0	—	235.0	—	—
Initial BW, kg	254.8	(±8.6)	251.3	(±8.64)	245.3	(±8.57)	0.73
Final BW, kg	662.3	(±10.91)	656.7	(±10.9)	640.7	(±10.89)	0.63
ADG, kg/d	1.7	(±0.03)	1.73	(±0.03)	1.7	(±0.03)	0.42
HCW, kg	393.9	(±11.08)	397.59	(±11.0)	396.0	(±11.02)	0.86
HCW/final BW, %	60.7	(±0.80)	61.71	(±0.86)	61.8	(±0.86)	0.59
Ribeye area, cm^2	84.1	(±4.20)	79.63	(±4.25)	76.9	(±4.15)	0.37
Fat over 12th rib, cm	1.3	(±0.14)	1.40	(±0.14)	1.3	(±0.14)	0.58
USDA YG	3.1	(±0.31)	3.44	(±0.31)	3.2	(±0.31)	0.36
Marbling score	471.1	(±23.69)	463.37	(±23.23)	454.5	(±23.84)	0.65

Mean values for total days in the feedlot, initial and final BW, ADG, and carcass characteristics by treatment group.

USDA = United States Department of Agriculture.

*Significance was defined at $P \leq 0.05$. — indicates that groups were not analyzed statistically.

Table 5. Comparison of orally administered arrival meloxicam (AMEL), or orally administered pretransport meloxicam (PMEL) to control treated steer (CONT) means (±SEM)

	MEL		CONT		
Variable	Mean	(±SEM)	Mean	(±SEM)	*P*-value*
Total days in the feedlot	235.0	—	235.0	—	—
Dry matter intake, kg	7.5	(±0.06)	7.6	(±0.1)	0.64
ADG, kg/d	1.7	(±0.02)	1.7	(±0.03)	0.19
HCW, kg	396.0	(±11.00)	396.2	(±11.0)	0.98
HCW/final BW, %	61.2	(±0.58)	61.8	(±0.9)	0.54
Ribeye area, cm^2	88.4	(±3.79)	87.1	(±4.1)	0.64
Fat over 12th rib, cm	1.4	(±0.12)	1.3	(±0.1)	0.37
USDA YG	3.3	(±0.29)	3.3	(±0.3)	0.68
Marbling score	467.4	(±21.60)	455.3	(±23.7)	0.44

Mean values for total days in the feedlot, initial and final BW, ADG, and carcass characteristics for animals in the MEL and CONT treatment groups.

USDA = United States Department of Agriculture.

*Significance was defined at $P \leq 0.05$ and trends are indicated by $P \leq 0.10$. — indicates that groups were not analyzed statistically.

stressor events to decrease the innate and adaptive immune response to BRD (Ackermann et al., 2010; Caswell, 2014). When purchased, these calves were deemed high risk, however, they did not encounter the same pattern of high morbidity that we anticipated. Calves identified as high risk can have group morbidities of 65 to 80% of the incoming comingled herd (Edwards, 2010). Our incoming cohort only experienced between 24.5 to 29.0% of BRD treatment. The lower morbidity of the study cohorts as well as potential issues of limited sample size can explain our inability to find statistically significant differences between treatment groups, however, there is still a scientific benefit to relay the importance of these findings when investigating NSAID therapy as a sole option for prevention of BRD.

In a field study, meloxicam used as a standalone treatment for BRD resulted in greater weight gain over the feeding period and a decrease in lung lesions at slaughter when compared to control animals (Friton et al., 2005). Meloxicam is shown to increase cow comfort after major surgery (Barrier et al., 2014). Additionally, the kinetics of meloxicam allows a singular administration to provide 3 d of therapeutic benefit in comparison to 3 consecutive days of flunixin meglumine treatment (Friton et al., 2004). Meloxicam provides added benefits for receiving performance (Guarnieri Filho et al., 2014). Presumably this additional performance on arrival is attributed to pain and stress relief. Due to these literature findings, we hypothesized that meloxicam administration, either prior to transport or on arrival, would decrease the severity of BRD morbidity for incoming high-risk calves through the reduction of pain, stress, and added performance. In the current study, however, there were no significant differences between animals that received the meloxicam before or after transportation on the incoming first treatment for BRD or treatments that were isolated to the first 10 d. Additionally, those animals that became clinical did not have any reduction of temperature when treated with meloxicam prior to shipment or on arrival. Severity score was also similar between the PMEL, AMEL, and CONT groups. Most of the respiratory disease encountered within the feedlot

Table 6. Comparison of orally administered arrival meloxicam (AMEL), or orally administered pretransport meloxicam (PMEL) to control treated steer (CONT) means (±SEM)

		AMEL		PMEL		CONT		*P*-value*		
Variable, unit	Time, days	Mean	(±SEM)	Mean	(±SEM)	Mean	(±SEM)	Treatment	Time	Interaction
Biomarker										
Cortisol, ng/mL	−1	36.9	(±1.10)	35.7	(±1.09)	35.9	(±1.10)	0.78	0.51	0.69
	0	37.9	(±1.10)	35.2	(±1.09)	40.1	(±1.10)			
Hp-MMP9, ng/mL	−1	0.5	(±0.35)	1.1	(±0.33)	0.7	(±0.35)	0.75	0.0015	0.28
	0	1.7	(±0.35)	1.5	(±0.33)	1.4	(±0.35)			
Substance P, pg/mL	−1	76. 9	(±1.29)	78.5	(±1.29)	70.1	(±1.29)	0.14	<0.0001	0.90
	0	87.2	(±1.29)	89.3	(±1.29)	80.5	(±1.29)			

Mean values for biomarkers analyzed on days −1 and 0 by treatment group.

*Significance was defined at $P \leq 0.05$. Same letters between groups indicate no significant differences between groups. Cortisol, Hp-MMP9 and Substance P were all quantified from blood samples.

was mild to moderate in severity. A study consisting of an induced BRD model also reported the lack of an effect of meloxicam treatment on behavior and clinical signs (Toaff-Rosenstein et al., 2016). Differences of severity in BRD were one of the suggested means of masking of potential positive or negative effects (Toaff-Rosenstein et al., 2016). Based on our study findings, we would not advise the use of meloxicam as a pre transport or on arrival standalone management practice for BRD and use of NSAIDs in the combination with an antibiotic approved for use against BRD have shown mixed results.

Meloxicam use in food animals falls under the animal medicinal drug use clarification act of 1994 as extra label drug use. However, it remains important to stress that the sole use of meloxicam for production purposes is not allowed under the animal medicinal drug use clarification act of 1994. In addition, these drugs may not be used in feed and a violative residue is prohibited since the drug has no labeled approval for use in cattle and no drug tolerance has been established by the FDA (U.S. Food and Drug Administration, 2018). We hypothesized that the use of meloxicam to reduce pain and stress prior to transport or on arrival would have beneficial effects on ADG, DMI, and G:F at 42 d. Justification for this hypothesis originated from previous research suggesting dairy calves treated with meloxicam, prior to the stress of dehorning, spent more time standing at the feed bunk, and gained weight (Coetzee et al., 2012b; Theurer et al., 2012). There were multiple differences in age and weight of the animals as well as difference in production management. Also, these animals were handled more often and may have encountered more artificial stressor events. In our study, all 3 groups gained significant weight during the first 42 d. There was no added treatment benefit for ADG, DMI, or G:F between day 0 and 42. Previous authors have indicated a meloxicam effect for decreasing the shrink associated losses in the first week and additional benefits for increased ADG and G:F over the 21 d after arrival when comparing meloxicam treated groups to the transport controls (Guarnieri Filho et al., 2014). However, these authors did not report data beyond 21 d. Our results indicate that compensatory gain negates potential original performance benefit in the first 21 d. Flunixin meglumine, another NSAID labeled for pyrexia in cattle, has also been investigated at cattle receiving after long distance transportation. This therapeutic option did not improve any receiving performance of the feeder cattle over 28 d (Cooke et al., 2013a). This is not surprising considering events such as castration can decrease the ADG and G:F within the first 14 d, however, effects at day 28 were not detected (Coetzee et al., 2012a). Other evidence is apparent that ADG, even in week old calves, does not support added benefits despite indication of potential reduction of pain through observable behavioral changes (Melendez et al., 2018).

Carcass performance is generally influenced by management decisions made upon arrival of cattle at the feedlot. Initial processing decisions such as metaphylaxis (Tennant et al., 2014) or vaccination (Wildman et al., 2008) can make a difference at harvest. Disease-related inflammation can have negative effects on harvest through partitioning of energy sources to catabolic processes associated with immune function and the acute phase proteins (Gifford et al., 2012). We hypothesized that use of meloxicam would be beneficial in reducing subclinical inflammation associated with transport. NSAID treatment, however, on arrival or prior to transport did not significantly influence the majority of carcass performance parameters. Other investigators have described a lack of benefit

on carcass characteristics when using NSAID as ancillary therapy to BRD treatment in feedlot cattle (Wilson et al., 2015). There may be a difference in outcome based on the time of administration prophylactically versus at diagnosis or type of NSAID. Benefits at harvest can lead to premiums if cattle are marketed appropriately on grid pricing (Fausti et al., 2014). A singular oral meloxicam dose during a time of inflammation has improved lactation in the dairy cow after postpartum administration (Carpenter et al., 2016). In addition, the hypothesis of an increased performance at arrival as described by Guarnieri Filho et al., (2014) could potentiate the lingering drug benefits. However, we acknowledge measurements were not recorded on days 7 and 21 postarrival due to some logistical and personnel constraints.

Measuring biomarkers prior to and after transportation has been done extensively. In this manuscript, we chose biomarkers based on indication for stress(Ali-Gholi et al., 2007), pain(DeVane, 2001), and correlation to BRD (Bannikov et al., 2011; Senthilkumaran et al., 2013). We did not pursue other time points which is a drastic shortcoming of potential interpretation however, multiple timepoints would have interfered with gains, efficiency and added stress could have potentially confounded the disease process.

Cortisol is a commonly investigated glucocorticoid hormone that is used as an indicator of stress during and after transportation (Chacon et al., 2005). Previous investigation confirmed that cortisol release was inversely proportional to meloxicam concentrations and was critical in reduction of the stress leukogram (Van Engen et al., 2014). We hypothesized that treatment with meloxicam would result in a reduction of cortisol for PMEL. Cortisol levels follow a natural circadian rhythm (Van Cauter et al., 1996) and can vary by cattle production type and breed. Despite the lack of significant changes in cortisol over time and by treatment group, we would not attribute this to a lack of stress during transport. Animals in the control group had higher cortisol levels on arrival (40.17 ± 1.10 ng/mL) when compared to PMEL-treated animals (35.22 ± 1.10 ng/mL) and AMEL animals (37.91 ± 1.10 ng/mL). Perhaps, we missed the peaks in cortisol levels during the observation times we used in this study.

Substance P is a neurotransmitter stored in the dorsal horn of the spinal cord and released in response to cutaneous noxious stimuli (DeVane, 2001). In calves, plasma concentrations of substance P have been considered a potential biomarker of pain following castration (Coetzee et al., 2008). An increase in circulating levels has been found to be inversely proportional to meloxicam concentrations after scoop dehorning (Coetzee et al., 2012b). These findings suggest an analgesic benefit of NSAID therapeutics. Transportation has been described to increase the levels of circulating substance P (Van Engen et al., 2014). We hypothesized there would be an increased substance P at arrival. The present study's cohorts had a significant increase in substance P over time. This is consistent with the findings from a previous trial (Van Engen et al., 2014). We also hypothesized a decrease in substance P for animals in the PMEL group when compared to AMEL and CONT. However, no significant treatment effects were detected. When comparing circulating substance P levels, the concentrations of substance P in our study animals were drastically lower than those involving incisional castration (506.43 ± 38.11 pg/mL) and even drastically lower than in uncastrated controls (386.42 ± 40.09 pg/mL) (Coetzee et al., 2008). Despite the differences in diagnostic test used, the percent change of substance P from baseline to post castration or transportation event in these 2 studies is also markedly different. Potentially, meloxicam is less efficacious when there is no specific pain response. Investigating substance P as a marker of pain in a transport is still warranted from an animal welfare standpoint or lack of sampling timepoints could have missed the difference in substance P response. A previous study supports the hypothesis that transportation induces more likely a stress response than a pain response(Marti et al., 2017), however, a combination of the 2 is still highly plausible based on cattle handling, temperament, and transport methods.

Hp- MMP-9 complexes released in response to acute inflammation are useful at identifying pulmonary inflammation; as described in a previous challenge model (Hanthorn et al., 2014). Haptoglobin has been investigated in transport studies as part of the acute phase protein response during weaning and transport of cattle (Arthington et al., 2003; Carroll et al., 2009). This acute phase protein is produced primarily by the liver, with minor amounts produced by other tissues. However, a superior indicator of inflammation associated with BRD is a complex of Hp-MMP-9 in comparison to either Hp or MMP-9 individually (Bannikov et al., 2011). These markers (Hp-MMP-9) only identified source is from neutrophils, which play a prominent role in acute inflammation associated with BRD (Slocombe et al., 1985). As an indicator of inflammation associated with disease, we hypothesized that there would

be an increase of Hp-MMP-9 over time and a decrease in the Hp-MMP-9 levels for animals treated with meloxicam. We did find a significant increase over time for circulating Hp-MMP-9. However, there was no significant meloxicam effect in reducing the biomarker in circulation, which is consistent with previous work (Van Engen et al., 2014). Though Hp-MMP-9 has been validated as a marker of pulmonary inflammation, using haptoglobin alone as an early indication of BRD on arrival has limited utility in deciding BRD treatment methods (Holland et al., 2011). Our study findings and past results of meloxicam's minimal effect on Hp-MMP-9, were not surprising. It is necessary to identify Hp-MMP-9 responses of different animal cohorts in different scenarios such as transportation to identify potential correlation to disease. Reasons for the absence of significant association between haptoglobin with BRD morbidity may have been due to the lower percentage of BRD cases compared to Holland et al.'s (2011) investigation of haptoglobin as a predictor, and our lack of high severity BRD scores or the limited sampling timepoint to indicate a progression of the BRD progression. Using this marker still has utility in assessing inflammation.

When the aforementioned biomarkers were chosen for investigation, we hypothesized a significant correlation with BRD outcomes. Investigation examined biomarkers singularly and in combination for indication of sickness in incoming feedlot calves. Likely due to the low BRD morbidity observed, there was no significant correlation of these biomarkers with BRD sickness.

In conclusion, meloxicam administered prior to transportation or on arrival had no significant effect on the number of BRD cases. Incoming calves that developed clinical BRD did not differ in time to treatment or in rectal temperature compared to untreated controls. Additionally, there was no significant effect on ADG or G:F at 42 d on feed. ADG at the final day of the feeding period and carcass characteristics did not differ between groups. Circulating biomarkers are generally affected by events such as transportation. No significant treatment effects on transportation biomarkers were noted in the present study. The absence of statistically significant evidence could be due to limited sampling timepoints, sample size, and lower than anticipated BRD morbidity in this population. Caution should be taken with interpretation for this study Budgetary and personnel constraints limited the number of sampling time points in the study. Meloxicam should still be considered as an option for ancillary treatment when considering the welfare of the animal; however, continued research into its potential benefit when administered in tandem with antibiotic therapeutics for BRD is necessary.

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