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Behavioral and performance response associated with administration of intravenous flunixin meglumine or oral meloxicam immediately prior to surgical castration in bull calves

Charley A. Cull,[†,‡,1] Darrel J. Rezac,[†] Keith D. DeDonder,[†] Jon E. Seagren,[‡] Brooke J. Cull,[†,‡] Vijay K. Singu,[‖] Miles E. Theurer,[$] Miriam Martin,[¶] Raghavendra G. Amachawadi,[¶] Michael D. Kleinhenz,[¶] and Kelly F. Lechtenberg[†,‡]

[†]Veterinary and Biomedical Research Center, Inc., Manhattan, KS 66502, USA
[‡]Midwest Veterinary Services, Inc., Oakland, NE 68045, USA
[‖]CSRC Veterinary Diagnostic Laboratory, Oakland, NE 68045, USA
[$]Veterinary Research and Consulting Services, LLC, Wellington, KS 67152, USA
[¶]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA

[1]Corresponding author: charley@mvsinc.net

Abstract

The objective of this study was to determine the effects of flunixin meglumine or meloxicam on behavioral response and performance characteristics associated with surgical castration in crossbred bulls. Intact male *Bos taurus* calves (n = 252; averaging 176 kg) were randomly allocated into one of three treatment groups within pen: control (**CON**), flunixin meglumine (**FLU**; 2.2 mg/kg intravenous injection), or meloxicam (**MEL**; 2.0 mg/kg *per os*). The individual animal was the experimental unit. Calves were individually weighed on days 0 and 14 of the trial to evaluate performance outcomes. On study day 0, treatments were administered, according to their random allocation, immediately prior to surgical castration using the Henderson tool method. Visual analog scale (**VAS**) assessment and categorical attitude score (**CAS**) were collected on days −1, 0 (6 h post-castration), 1, 2, 3, and 4 in the study. The VAS was assigned using a 100 mm horizontal line with "normal" labeled at one end of the line and "moribund" at the other end of the horizontal line. The masked observer assigned a mark on the horizontal line based upon the observed severity of pain exhibited by that individual animal. The CAS was assigned by the same observer using five different categories with a score of 0 being "normal". Average daily gain tended (P = 0.09) to be associated with the treatment group, and MEL had a greater (P = 0.04) average daily gain through day 14 compared with CON. A significant (P < 0.01) treatment by day interaction was indicated for VAS score, and MEL had lower VAS scores on days 0, 1, 2, and 3 post-castration compared with CON; FLU had lower VAS scores on days 0 and 1 compared with CON. A significant treatment by day interaction was not present (P = 0.25) for CAS. The FLU had lesser percent CAS ≥1 (17.5%; P = 0.05) compared with CON (29.4%); MEL has lesser percent CAS ≥1 observations (14.9%; P = 0.01) compared with CON. The median VAS increased as CAS was more severe. Results indicated MEL and FLU calves temporally improved behavioral responses following surgical castration with positive numerical trends for a 14 d average daily gain (ADG). The VAS system appeared to be an effective method of subjective evaluation of pain in beef calves in this study. Route of administration, duration of therapy, and low relative cost make oral meloxicam a reasonable analgesic treatment in calves when administered at the time of surgical castration.

Key words: analgesia, beef cattle, castration, flunixin meglumine, meloxicam, welfare

Abbreviations: AMDUCA, Animal Medical Drug Use and Clarification Act; AVMA, American Veterinary Medical Association; CAS, categorical attitude score; CON, control; FLU, flunixin meglumine; IACUC, Institutional Animal Care and Use Committee; MEL, meloxicam; NSAID, nonsteroidal anti-inflammatory drugs; PO, *per os*; US FDA, United States Food Drug Administration; VAS, visual analog scale

Introduction

Castration has been recognized as one of the most common surgical procedures performed on bull calves, with an estimated 16 million calves castrated every year in the United States (USDA, 2016). Calves are castrated in the beef industry to reduce aggression and behavioral responses, improve carcass quality, and prevent unwanted pregnancy (Stafford and Mellor, 2005; Coetzee, 2013). Castration of bull calves is considered a painful procedure for beef calves but routinely performed without analgesia (Coetzee et al., 2010; Fajt et al., 2011). As emphasis increases for the administration of an analgesic therapy with castration procedures, extra-label therapy is needed due to the lack of an approved food animal analgesic compound labeled for castration in the United States (U.S. Food and Drug Administration, 2006).

Previous literature has evaluated the effects of two commercially available nonsteroidal anti-inflammatory drugs (NSAID), flunixin meglumine and meloxicam, prior to castration in calves (Coetzee et al., 2012; Stock and Coetzee, 2015). Flunixin meglumine is an NSAID approved for intravenous

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route of administration and the control of pyrexia associated with bovine respiratory disease and inflammation associated with endotoxemia in food animals in the United States (Smith et al., 2008; Smith, 2013). A transdermal flunixin formulation has recently been approved by the United States Food Drug Administration (US FDA) for the control of pain associated with foot rot in cattle (FDA, 2017). Meloxicam is a relatively selective NSAID, preferentially inhibiting the COX-2 isoenzyme, approved to alleviate pain and inflammation following surgical and band castration in cattle in Canada (Engelhardt et al., 1996; https://solvet.ca/wp-content/uploads/2019/11/SOL-Meloxicam-Oral-Suspension-USP-CVP.pdf). However, no approved food animal analgesic compounds are indicated for castration-related pain in the United States. The onset of therapeutic activity is similar between oral and subcutaneous routes of administration for meloxicam but indicates a higher bioavailability with the oral route of administration (Coetzee et al., 2009). Although the literature indicates a potential behavioral or performance benefit of these products, a need exists for a more externally valid model of evaluation in a commercial beef production setting. Therefore, the objective of this study was to determine the effects of flunixin meglumine or meloxicam in comparison to the negative control, when administered at the time of surgical castration, on the behavioral characteristics and performance in crossbred bull calves.

Materials and Methods

All activities related to this study were reviewed and approved by the Institutional Animal Care and Use Committee of the Veterinary and Biomedical Research Center, Inc. prior to study initiation (IACUC number VAC15024B).

Study population and animal management

A total of 252, intact male crossbred *Bos taurus* calves (mean ± SE BW = 176 ± 4.7 kg) were received into a commercial backgrounding yard in Kansas. Each animal was identified by an individual ear tag. Individual cattle were eligible for inclusion if they had a categorical attitude score (**CAS**; Table 1) of 0, presence of two descended testicles, and a minimum of a 30 d acclimation period. Following a brief transition period, cattle were fed once daily, a grower diet which included (as-fed basis): 52.7% wet distillers' grain, 37.6% roughage, 8.4% cracked corn, and 1.3% micro/minerals mix (including 200 mg of monensin per animal per day [Rumensin, Elanco Animal Health, Greenfield, IN]). Standard operating procedures at the backgrounding yard were followed for cattle management and care.

Treatment allocation and administration

Individual animals were randomly allocated using computer software (Excel, Microsoft Corp., Redmond, WA) to one of three treatment groups within pen (n = 5 pens): control (**CON**), flunixin meglumine (**FLU**; 2.2 mg/kg BW via jugular intravenous injection), or meloxicam (**MEL**; 2.0 mg/kg BW *per os*). Treatments were administered immediately prior to castration on study day 0.

CON was administered 0.9% sodium chloride (0.044 mL/kg BW via jugular intravenous injection) and whey protein powder (approximately 14 g, *per os*). The whey protein powder dose amount was selected as this was proximate to the average weight of the MEL test article (meloxicam) as supplied by 7.5 mg meloxicam tablets (Zydus Pharmaceuticals USA, Inc., Pennington, NJ) within a porcine gelatin capsule. Both meloxicam and whey powder were delivered to the respective treatment groups via a single, 24 mL porcine gelatin capsule (Torpac, Inc., Fairfield, NJ) using a commercially available stainless steel balling gun. Meloxicam doses were rounded to the next (higher) nearest 7.5 mg (whole tablet) dose. The FLU group also received whey protein (approximately 14 g, *per os*) and MEL, 0.9% sodium chloride (0.044 mL/kg BW) via jugular intravenous injection to ensure each animal received similar procedural manipulations, regardless of treatment group. All intravenous injections were administered through the jugular vein using an 18 gauge × 40 mm hypodermic needle.

Castration procedure

Castration was completed on study day 0, immediately after (approximately 30 s) the treatment administration while the animals were restrained in a hydraulic chute (Silencer Chutes, Moly Manufacturing, Inc., Lorraine, KS). Briefly, all foreign material was removed from the scrotum by a gloved hand and the scrotum was thoroughly scrubbed with a dilute chlorhexidine solution. Both testicles were isolated near the body wall, and the scrotum was incised using a Newberry knife (Jorgensen Lab, Loveland, CO). Approximately 50% of the length of the scrotum was incised perpendicular to the scrotal septum to expose both testicles with a single incision, and allow for adequate drainage during healing. The cremaster muscle of each testicle was broken down by blunt dissection, and the Henderson castration tool (Stone Manufacturing and Supply Company, Kansas City, MO) connected to a cordless

Table 1. Description of CAS to classify pain status of calves castrated using the Henderson tool technique and administered injectable flunixin meglumine, oral meloxicam or a sham control at the time of castration

Categorical attitude score (CAS)	Description	Clinical appearance
0	Clinically normal	Stands and walks normally, no aversion to movement, appears bright and alert
1	Mild depression	Appears slightly depressed, but responds quickly to handler when prompted
2	Moderate depression	Head lowered, ears drooped, animal moves away slowly from handler when prompted
3	Severe depression	Head lowered, ears drooped, animal is reluctant to move away from handler when prompted, appears to have low abdominal fill
4	Moribund	Animal will not rise or move without kinetic pressure from handler. Animal is a candidate for humane euthanasia upon consultation with attending veterinarian

drill was clamped to the spermatic cord proximal to the head of the epididymis. The electric drill was engaged in a clockwise direction to twist the spermatic cord until severed by spiral torsion as previously described (Coetzee et al., 2007; Webster et al., 2013). The same procedure was used to remove the second testicle. After removal of both testicles, the scrotum was disinfected with 1% iodine wound spray. The Henderson castration tool was disinfected with dilute chlorhexidine solution between each animal.

Outcome measures and blinding

A single observer, blinded to treatment group allocation, subjectively evaluated the bulls with each treatment equally represented on study days −1, 0 (6 h post-castration), 1, 2, 3, and 4 of the study. The observer was a trained DVM with vast experience in visual analog scale (**VAS**) scoring in cattle models. Observations were recorded at 08:00 a.m. daily with the observer standing in the pen. All animals were observed at each timepoint and scoring was completed while in the pen. The observer used the VAS and CAS as assessment methods for each animal evaluated at each time point. The VAS was assigned using a 100 mm horizontal line with "normal" labeled on the left end of the line and "moribund" at the right end of the horizontal line. A vertical mark was placed on the VAS line at the point, which in the blinded evaluator's assessment, reflected the pain status of the animal between normal and moribund. The distance the observer marked on the horizontal line was measured with the use of a digital caliper (Fisher Scientific, Hampton, NH) to derive the raw data point for inclusion into the dataset. The CAS was assigned using a five-point scoring system defined in Table 1 just after the VAS was determined.

Cattle performance measures were considered secondary outcomes and were collected by study personnel also blinded to the treatment group. Furthermore, personnel who administered treatments did not collect VAS, CAS, health, or performance data. Cattles were individually weighed on days 0 and 14 of the study. For purposes of this study, ADG was calculated as:

$$\text{ADG} = (\text{Day14Day 0}) \ /14 \text{ days}$$

Statistical analysis

Data were entered into a commercial software package (R Core Team 2015, Vienna, Australia). The VAS was evaluated as the proportion of scale an individual calf was scored at each observation period (Myles et al., 1999). A binary outcome variable was created for each animal for CAS. Calves receiving a CAS ≥ 1 were assigned a value of 1, and calves that received a CAS equal to 1 were assigned a value of 0. Generalized linear mixed models were used for the VAS and CAS outcomes and included treatment group, study day, and treatment by study day interaction. Random effects for repeated measures on individual calves within a pen were included for the VAS and CAS outcomes. Due to study design, the biological plausibility of castration pain, and outcome of interest, if treatment by study day interaction was not statistically significant ($P > 0.10$), day was included as a random effect in the final statistical model to evaluate the overall treatment effects. Effects with a P-value ≤0.10 were further explored. Potential differences within an individual study day between treatment groups were evaluated with pairwise comparisons. A P-value ≤0.05 was considered statistically significant for all pairwise comparisons. Box and whisker plots with median, first and third quartiles, minimum, and maximum VAS by CAS were evaluated. Continuous outcomes of initial BW and ADG were evaluated with individual mixed linear models. Linear models included a random effect for pen in analysis and treatment as a fixed effect.

Results

There was a ($P < 0.01$) treatment by study day interaction for VAS (Figure 1). Calves in the MEL group had decreased VAS scores on days 0 ($P = 0.07$), 1 ($P < 0.01$), 2 ($P = 0.05$), and 3 ($P = 0.01$) compared with CON calves. Calves in the FLU group had decreased VAS scores on days 0 ($P < 0.01$) and 1 ($P < 0.01$) compared with CON calves. No other comparisons among treatment groups within a day were statistically significant for VAS.

There was not a treatment by study day interaction for CAS. Study day remained in the final model as a random effect due to study design. Calves in the MEL group had decreased percentage of CAS ≥ 1 ($P = 0.01$) compared with CON calves (Figure 2). Calves in the FLU group had decreased percentage of CAS ≥ 1 ($P = 0.05$) compared with CON calves (Figure 2). No differences were identified in the percentage of CAS ≥ 1 in MEL group compared with FLU group ($P = 0.58$). Box and whisker plots of VAS by CAS were displayed in Figure 3.

Average daily gain during the first 14 d after surgical castration tended ($P = 0.09$) to be associated with the treatment group. Average daily gain (± SE) of calves in the CON, FLU, and MEL treatment groups were 1.20 (± 0.31), 1.23 (± 0.31), and 1.40 (± 0.31) kg/day, respectively. Calves in the MEL group had greater ADG compared with CON calves from day 0 to day 14 ($P = 0.04$); MEL calves also tended ($P = 0.09$) to have greater ADG from day 0 to day 14 compared with FLU calves. No differences ($P = 0.72$) were identified in ADG for CON compared with FLU calves.

Discussion

The objective of this study was to evaluate the use of two of the most commonly prescribed NSAID products, utilizing an experimental model that closely resembled those practices which are commonly employed at commercial cattle feeding facilities. Based on these data, it seems clear that pain-associated behavior traits were diminished by both MEL and FLU; however, differences were also elucidated between their therapeutic duration, which is consistent with current data relating to the pharmacokinetic profile of oral meloxicam and intravenous flunixin meglumine (Coetzee, 2013; Fraccaro et al., 2013).

The American Veterinary Medical Association (AVMA) policy on castration and dehorning states that because these procedures cause pain and discomfort, practices such as the use of the Animal Medical Drug Use and Clarification Act (AMDUCA)-permissible clinically effective medications are recommended when possible (AVMA, 2019). Injectable flunixin meglumine is, at current, only labeled for intravenous administration in cattle, though anecdotal reports suggest that it is widely known within the veterinary community, however, that injectable flunixin meglumine is often administered via non-approved routes (intramuscularly or subcutaneously) by personnel who are not

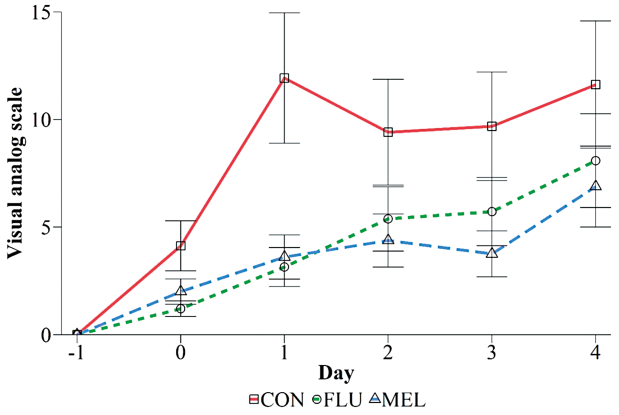

Figure 1. Model-adjusted least squares means (± SE) of VAS scores by treatment group and study day of calves castrated using the Henderson tool technique and concurrently administered injectable flunixin meglumine (FLU; 2.2 mg/kg BW via jugular intravenous injection), oral meloxicam (MEL; 2.0 mg/kg BW *per os*), or sham control products (CON) at the time of castration. The model included effects for repeated measures on individual calves within pen. Calves in the MEL group had decreased VAS scores on days 0 ($P = 0.07$), 1 ($P < 0.01$), 2 ($P = 0.05$), and 3 ($P = 0.01$) compared with CON calves. Calves in the FLU group had decreased VAS scores on days 0 ($P < 0.01$) and 1 ($P < 0.01$) compared with CON calves. No other comparisons among treatment groups, within a day were statistically significant for VAS.

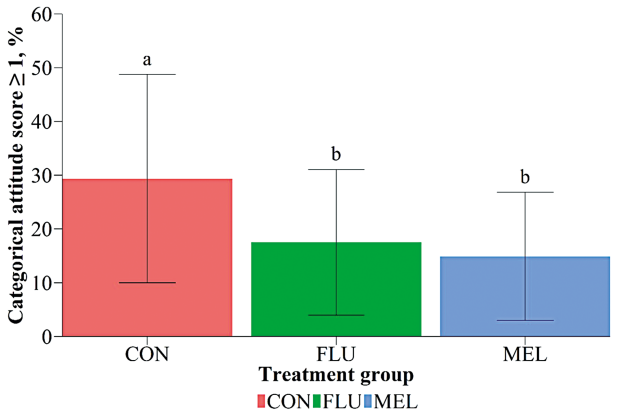

Figure 2. Model-adjusted least squares mean (±SE) percentage of CAS ≥1 observations by treatment group of calves castrated using the Henderson tool technique and concurrently administered injectable flunixin meglumine (FLU; 2.2 mg/kg BW via jugular intravenous injection), oral meloxicam (MEL; 2.0 mg/kg BW *per os*), or sham control products (CON) at the time of castration. The model included effects for repeated measures on individual calves within pen. The model included random effects for repeated measures on individual calves within pen and study day. Treatment groups not connected by the same letter are significantly ($P < 0.05$) different.

proficient at intravenous jugular injection techniques. It is worth noting that altering the route of administration is not a justifiable basis for ELDU, and is considered illegal by the Animal Medical Drug Use Clarification Act (AMDUCA) and may cause local tissue reactions (U.S. Food and Drug Administration, 2014). This risk factor, along with the overall time required to intravenously administer the product, demonstrates a significant drawback to the use of injectable flunixin meglumine as an analgesic at the time of castration.

Currently, meloxicam is not labeled for use in cattle, for any indication or by any route of administration in the United

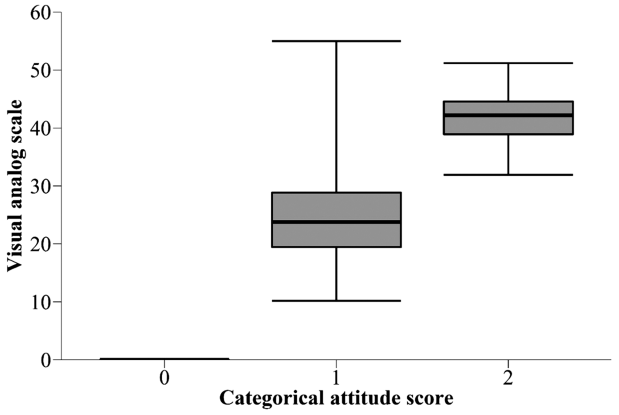

Figure 3. Box and whisker plots with median, first and third quartiles, minimum, and maximum VAS by CAS that were surgically castrated using the Henderson tool technique.

States, and, as previously stated at this time, there are no products labeled for analgesia in cattle at the time of castration. Taken as a whole, these factors justify the extra-label use of meloxicam under AMDUCA. One clear advantage to meloxicam over that of an injectable NSAID is the ability for the therapeutic to be administered *per os* (PO) as a single bolus, which requires much less training and skill to become proficient at as compared with intravenous administration techniques, while also decreasing the time required for administration, thus potentially also decreasing the amount of time the animal is restrained. Furthermore, administering therapy PO decreases, the number of injections the animal is subjected to, which is in compliance with initiatives such as the Beef Quality Assurance program (Beef Quality Assurance, 2014).

A final key consideration must be the cost/benefit model of providing therapeutic analgesia. The cost of pain mitigation is a common factor identified by producers, which has affected the widespread adoption into the industry (Newton and O'Connor, 2013). A survey of practicing veterinarians in North America identified only 21% of respondents administered a systemic analgesic compound at the time of castration with flunixin meglumine being the most common product used. At the time of this study, the cost of meloxicam was $0.40/100 kg of BW and the cost of flunixin meglumine was $0.93/100 kg of BW.

Some of the previous publications utilizing meloxicam have described a protocol where the treatment was administered approximately 24 h prior to the painful procedure (e.g., dehorning and castration; Coetzee et al., 2012), under that hypothesis this lead time was required to allow for the maximum therapeutic effect at the time of the painful procedure (the time to maximum plasma concentration is 12 to 24 h for meloxicam; Coetzee et al., 2009; Fraccaro et al., 2013). However, administering meloxicam to calves 24 h prior is wrought with many inefficiencies and is not likely an externally valid model. An additional day processing calves through a chute requires extra time, labor, is an additional stressor for the cattle, and has been identified as a potential reason for decreased animal performance (Voisinet et al., 1997; Cull et al., 2012, 2015; Francisco et al., 2012). In the current study, both the MEL and FLU treatment groups were administered immediately prior to surgical castration which represents a scenario more likely to be adopted by producers and recommended by veterinarians.

The modest ADG improvement observed in the current study for MEL and FLU vs. CON was unexpected. Previous research has indicated calves dehorned and administered meloxicam spent more time near the feeder compared with placebo control calves which may be a potential reason for improved ADG in the current study (Theurer et al., 2012). Healthy animals also spent more time near the feeder compared with morbid animals (Sowell et al., 1999; Buhman et al., 2000; Theurer et al., 2013b; Jackson et al., 2016). A meta-analysis, which investigated the association between pain management and increased production outcomes, concluded that the body of work does not support the hypothesis of analgesics/pain interventions directly improving performance parameters (Newton and O'Connor, 2013). Newton and O'Connor (2013) also point out that the vast majority of the published data in this field are associated with short study periods and a relatively low number of experimental units. The study herein was short in duration, mostly attributable to the stage of production, but had a sample size much larger than many previous publications. The production benefits observed in this study are modest but do suggest that this topic warrants further investigation.

Given the differences in the pharmacokinetics of the two drugs, an apparent longer duration of therapeutic effect in MEL compared with FLU was not surprising. The plasma half-life of meloxicam administered PO in calves has been shown to vary from 16 to 27 h (Wagner et al. 2021). In contrast, the reported half-life of flunixin meglumine administered intravenously ranges from 3 to 8 h in plasma (Anderson et al., 1990; Landoni et al., 1995; Coetzee et al., 2009; Fraccaro et al., 2013; Glynn et al., 2013). The longer plasma half-life of meloxicam compared with flunixin meglumine provides meloxicam a larger area under the curve which should reasonably translate to a longer period for potential analgesic therapeutic effect. Furthermore, the 2 mg/kg dose used in this study is double that previously published. It would be expected that the duration of effect for meloxicam would be an additional half-life and thus an additional 16 to 27 h. Further work is needed to better explain the effect a double dose may have on prostaglandin production.

Flunixin meglumine administered intravenously is deposited directly into the systemic circulation where it can potentially provide analgesia almost instantaneously, whereas an orally administered therapy, such as the meloxicam used in this study, must be absorbed through the gastrointestinal tract before it can enter the systemic circulation to provide analgesia. Thus, resulting in a lag time between the drug administration and its clinical therapeutic effect, therefore, it was not surprising that FLU anecdotally appeared to elicit a more immediate effect on pain behaviors as compared with MEL. However, it is important to note that there were no statistical differences observed between MEL and FLU.

Historically, scoring systems used for clinical evaluation have been based on discrete categorical outcomes, arranged in a loose ordinal system. Meaning that observers classify an animal into an individual category (or score) based upon the appearance and clinical signs of the animal. Results are tabulated but commonly are evaluated as binary outcomes to determine the probability of being classified as normal or abnormal (Theurer et al., 2013a). These types of scoring systems are much more qualitative in nature than they are quantitative, as the difference between each descriptive category is not necessarily the same. Additionally, the differences between each category can be interpreted to be of a different magnitude by different clinical scorers. In contrast, the VAS system provides a more sensitive scoring system to the observer. This continuous scale has the potential to more accurately identify and quantify subtle differences between treatments groups which may not be able to be captured with traditional categorical scoring systems (Welsh et al., 1993). The continuous VAS has been used to accurately and reliably identify dairy cows with sole ulcers in dairy cows (Flower and Weary, 2006). A VAS was utilized by two scorers to assess pain in cattle (steers and bulls) following processing at a feedyard (Martin et al., 2020). The authors reported a lower VAS for calves treated with transdermal flunixin. Furthermore, research in humans has identified that the VAS has the ability to accurately represent the magnitude of pain experienced in the human medical field (Myles et al., 1999).

In the current study, the similarities between the VAS and CAS ≥1 outcomes as well as the distribution of the VAS score by CAS demonstrate that the VAS system was an effective scoring tool in this group of calves. Based on these results, it seems prudent that the VAS system warrants further research as a subjective measure of pain exhibited by beef calves. However, it is important to note that while the observer assigning CAS and VAS scores was blinded to the treatment group, the same observer assigned the CAS and VAS scores to each calf individually at the same time. Therefore, it must be noted that the potential for observation bias to occur was present since the observer did not assign CAS and VAS independently, but rather did so simultaneously.

Conclusions

Data indicated that MEL and FLU both improved behavior response in calves after surgical castration. Even while considering the different routes of administration, both products improved behavior response when administered concurrently to the painful stimuli. The VAS system appears to be an effective method of pain-associated behavioral assessment in this class of animals. Average daily gains were improved when meloxicam was provided. Method of administration, duration of effect, and the cost of treatment make meloxicam an attractive analgesic in calves when administered at the time of surgical castration.

Acknowledgment

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Conflict of Interest Statement

The authors declare no real or perceived conflicts of interest.

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