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Authors
Newby, Nathalie C
Tucker, Cassandra B
Pearl, David L
et al.

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Article

An investigation of the effects of ketoprofen following rumen fistulation surgery in lactating dairy cows

Nathalie C. Newby, Cassandra B. Tucker, David L. Pearl, Stephen J. LeBlanc, Ken E. Leslie, Marina A.G. von Keyserlingk, Todd F. Duffield

Abstract — Post-operative pain management following rumen surgery is not common practice. We examined the effect of providing the pain medication ketoprofen to dairy cattle following the first stage of a rumen cannulation surgery, which involves an incision in the body wall and exteriorizing and clamping the rumen. The results of this study provide clear evidence that the first stage of the surgery was painful and ketoprofen at the time of and 24 h following surgery, alleviated some, but not all, of the post-surgical pain. Pain mitigation should be included when performing flank surgery in cattle.

Résumé — Une enquête sur les effets du kétoprofène administré à des vaches laitières après une chirurgie de fistulisation du rumen. Ce n'est pas pratique courante d'administrer des analgésiques suite à la chirurgie du rumen. Cette étude a examiné les effets du médicament kétoprofène chez les vaches laitières après la première étape d'une chirurgie de fistulisation du rumen. Cette chirurgie consiste à faire une incision sur le côté gauche de l'abdomen pour ensuite sortir une partie du rumen de l'abdomen et de le fixer avec une attache. Les résultats de cette étude démontrent que la première étape était douloureuse et que l'administration du kétoprofène, à la fin de la chirurgie, ainsi qu'après 24 h, a atténué une partie de la douleur chirurgicale sans toutefois l'enlever complètement. L'administration d'analgésiques devrait faire partie intégrante du traitement lors des chirurgies abdominales chez les bovins.

(Traduit par les auteurs)

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Introduction

Fistulation surgery of the rumen is a common scientific procedure used to investigate nutrition (1) and the effects of diet changes on rumen dynamics in cattle (2–5). The objective of this surgery is to facilitate access to the rumen by scientists interested in understanding the function of the ruminant digestive system. However, practitioners may occasionally do this surgery to provide a healthy rumen fluid resource within their practice or for their clients. Ruminants that have undergone fistulation surgery often also serve as important teaching tools at many universities, particularly for students interested in veterinary medicine, ruminant nutrition, anatomy, and physiology. This study was initiated because nutritionists at the University of Guelph required fistulated cows for their intensive nutritional research projects at the Elora Dairy Research Centre, University of Guelph, Guelph, Ontario. It also presented a unique opportunity to evaluate pain and pain management therapy following abdominal surgery in a controlled research environment.

The first component of this fistulation surgery is a left-flank laparotomy conducted under local anesthesia and involved clamping of the rumen wall to the skin. Studying pain following this stage might serve as a model for other more common laparotomy surgeries, such as left displaced abomasum correction or caesarean section. It is well-established that laparotomies are painful procedures in small animals (6). Pain relief agents are used in cattle during this type of procedure in Great Britain [e.g., 57% of veterinarians providing analgesia most commonly using non-steroidal anti-inflammatory drugs (NSAIDs) following laparotomies in 2000 (7)]. In a 2004–2005 Canadian survey, 96.8% of veterinarians providing analgesia most commonly used xylazine or lidocaine following omentopexy (8). However, the analgesic effects of xylazine and lidocaine are

Department of Population Medicine, University of Guelph, Guelph, Ontario N1G 2W1 (Newby, Pearl, LeBlanc, Leslie, Duffield); Department of Animal Science, University of California, Davis, California 95616-8521, USA (Tucker); Animal Welfare Program, University of British Columbia, Vancouver, British Columbia V6T 1Z4 (von Keyserlingk).

Address all correspondence to Dr. Todd Duffield; e-mail: tduffiel@uoguelph.ca

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Figure 1. The rumen pulled through the wooden clamp and sutured to the body wall on the left side of the animal. Gauze and tape are wrapped around the metal structures used to tighten the clamp to prevent any injury to the cow.

of short duration, between 15 to 30 min for xylazine (9) and approximately 90 min for lidocaine (10), and there was no mention of analgesia using NSAIDs for laparotomy surgery in the Canadian survey (8).

Although pain relief for this surgery has been reported [e.g., phenylbutazone postoperatively (5), flunixin meglumine pre-operatively and butorphanol post-operatively (11)] it is not a common practice. Furthermore, there have been no studies examining the effect of a post-operative analgesic following rumen fistulation on cow behavior and milk production.

The aims of this study were to evaluate the effects of providing an NSAID immediately following the first stage of a 2-stage fistulation surgery on physiological, behavioral, and production parameters in lactating dairy cows.

Materials and methods

Animals

Approval for this study was granted by the Animal Care Committee, University of Guelph (AUP# 09R044). Animals were housed at the Elora Dairy Research Centre (EDRC), University of Guelph. Cows were housed in individual tie-stalls (2.0 m × 1.2 m; bedding of wood shavings over mattresses filled with rubber crumbs) with feed dividers to allow for recording of feed intake beginning 7 d before surgery. This study was conducted between April and August 2009, with most cow pairs operated on between the end of April and end of June and 1 pair in mid-August. The mean temperature in the barn throughout the study was 18.5°C [± 2.8 standard deviation (SD)]. Randomly chosen cow pairs (because 2 surgical pens were available at a time) were moved to individual pens (3.5 m × 3.1 m; with either straw pack bedding or wood shavings over mattresses filled with rubber crumbs) the morning of surgery and remained in the pen for 7 d. All cow pairs were operated on between 09:00 am and 11:00 am on the day of the first stage of the fistulation surgery. The cows were then moved to recovering tie-stalls immediately following the second stage (cannula placement) for an additional week of observation before returning to their original designated tie-stall. Cows were milked twice daily at 05:00 and 15:00 in their stall or pen.

Cows were fed twice daily at 07:30 and 13:00 according to routine feeding procedures at the EDRC, except for the day of surgery when the morning feeding was delayed until after completion of the surgery (for both the first and second stages). Diets were fed as a total mixed ration (TMR) and contained haylage, corn silage, and hay for the forage base, and high moisture corn, protein, and mineral supplement for the concentrate. Samples of the diet were collected twice weekly and frozen at −20°C for later analysis. Dry matter intake (DMI) calculations were based on amount offered, orts, and dry matter analysis of sampled diets.

All clinical health events and treatments that may have occurred outside the surgery were recorded for each cow enrolled in the study. All cows were weighed upon enrolment in the study.

Fistulation surgery

The fistulation surgery for each animal was completed as a 2-stage procedure (12). The first stage consisted of a rumen clamp procedure, which began with clipping the hair and washing the left paralumbar fossa with iodine and alcohol solutions. Xylazine (Rompun; Bayer, Toronto, Ontario), 0.015 to 0.02 mg/kg body weight (BW), IV, was administered as a sedative 30 min before surgery and was followed by a proximal paravertebral block with 2% lidocaine (Zoetis Canada, Kirkland, Quebec). An adequate block was assessed by penetrating the skin a few millimeters at the surgical area with an 18-gauge needle to see if the cow reacted by moving or kicking or twitching the skin around the site. Following a satisfactory block and final skin preparation, a 20-cm vertical incision was made immediately behind the rib cage and 10 to 15 cm down from the transverse processes of the vertebrae. The rumen was pulled through the incision with towel clamps. Three vertical mattress sutures were placed on either side of the incision at the top, middle, and bottom, to later hold the wooden clamp in place. The rumen was held by 2 towel clamps at each end of the incision before being pulled through the wooden clamp. The clamp was then sutured tightly into place to the skin. The wooden clamp was tightened around the rumen and any metal parts from the clamp were covered in gauze and tape (Figure 1). The area around the clamp was cleaned and petroleum jelly was rubbed on the hide to prevent sores. Before releasing the cow from the head-gate, all cows received a dose of penicillin (Pen Aqueous; Zoetis Canada), 22 000 IU/kg BW, IV, and were either given the NSAID (see experimental protocol) or the saline injection.

The second stage of the fistulation procedure occurred 1 wk later and consisted of removing the clamp and placing a 7.62 cm diameter cannula (Bar Diamond; Parma, Idaho, USA) through the fistula and into the rumen. Details of this second stage are described elsewhere (12).

Experimental protocol

Eighteen healthy first lactation Holstein cows that were 293 ± 151 days in milk (DIM) and weighed 609 ± 52 kg (mean ± SD) were subjected to the 2-stage fistulation surgery.

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Table 1. Coefficient (β), 95% confidence interval (CI), and *P*-value for the variables of interest of either the Surgical Effect model or the Treatment Effect model for the different outcomes (DMI, milk production, time spent lying on the left side) for 18 late lactation Holstein cows assigned to receive ketoprofen (3 mg/kg BW), or saline (at an equivalent volume), by intramuscular injection at the time of first stage of a 2-stage fistulation surgery and 24 h later

Model	Outcome	Variable	β	95% CI	*P*-value
Surgical effect[a]	DMI (kg)	day 0	−2.5	−4.5, −0.62	0.01
		day 1	−3.1	−5.0, −1.1	0.002
	Milk production (kg)	day 0	−5.3	−7.8, −2.8	< 0.001
		day 1	−5.9	−8.4, −3.4	< 0.001
	Time spent lying on the left side (min/d)	day 0	−201.0	−286.7, −115.3	< 0.001
		day 1	−225.5	−311.2, −139.8	< 0.001
Treatment effect[a,b]	DMI (kg)	Ketoprofen	0.18	−2.4, 2.7	0.89
	Milk production (kg)	Ketoprofen	2.8	−0.34, 5.8	0.08
	Time spent lying on the left side (min/d)	Ketoprofen	119.1	11.8, 226.4	0.03

[a] While controlling for treatment and time as a categorical variable in all models, and for BW in the DMI and milk production models; pre-surgical values category was the referent for the time variable.
[b] While controlling for pre-surgical values as a covariate; saline was the referent for the treatment variable.

Enrolled cows were assigned in pairs based on their expected calving due date (mean due date difference ± SD = 12 ± 12 d) each week. Cows in each pair were randomly assigned to 1 of 2 treatments: 1) injection of ketoprofen (Anafen; Merial, Baie d'Urfé, Québec), 3 mg/kg BW, IM, or placebo (an equal volume of saline). Each cow received her respective treatment at the time of completion of the surgery (d 0), at 24 h post-surgery (d 1), on d 7 (at time of second stage of the procedure), and on d 8. There was blinding to treatment throughout the experiment, the data collection, and for the statistical analyses.

Daily feed intake and milk weights were recorded for 7 d pre-surgery and 7 d post-surgery. Other measurements were taken before surgery on d 0 (pre-surgical baselines), on d 1 (24 h following surgery prior to blood sampling and to second treatment), and on d 3, and d 7. These measurements included: heart rate, respiration rate, rectal temperature, infrared temperature readings (taken with a digital temperature reader; Mastercraft; Canadian Tire Corporation, Ontario) at 4 points around the surgical site (top, bottom, right and left, at 5 cm from the surgical site) and at a control point (at the edge of the shaved area by the L2 and L3 transverse processes). Blood samples were obtained by coccygeal venipuncture. The blood samples were taken in the morning, either pre-surgery or at approximately 2 h post-feeding (around 09:00) and pre-injection on day 1. The samples were allowed 1 h to clot, and then centrifuged for 15 min at 7000 × *g*. Serum was frozen and submitted for haptoglobin analysis to the Animal Health Laboratory, University of Guelph. All analyses were conducted using a Roche Cobas 6000 c501 automated chemistry analyzer (Roche Canada, Laval, Quebec). Haptoglobin concentrations were measured using the hemoglobin binding capacity, that used a methemoglobin reagent made on-site as described elsewhere (13,14). The analytical sensitivity of the haptoglobin assay was 0.03 g/L. The inter- and intra-assay coefficients of variation were 5.6% and 3.5%, respectively.

Behaviors were selected based on initial observations made from continuous video footage of 2 cows used in this study as well as behaviors identified in cattle during parturition (15) and on behaviors previously identified as indicative of laboratory animal pain (16,17). The behaviors analyzed by video included surgical site licking, non-surgical site licking, tail flicking (pendulous motion that resulted in hitting either the legs, flank, or back of the cow), and time spent at the feed bunk. These behaviors were monitored while the cows were housed in the individual pen using continuous video recordings obtained from a wide angle camera lens (Panasonic camera WV-CP504 and lens WV-LZA61/2S; Panasonic Canada, Mississauga, Ontario) connected to a recording system (GeoVision, UVS 1240E2; GeoVision, USAVisionSys, Irvine, California, USA). The individuals (n = 3) analyzing the video footage were blind to treatment (average for all behaviors inter-observer reliability r^2 = 0.90 and intra-observer reliability r^2 = 0.99, determined by analyzing the same randomly selected 2 h of video footage for a subset of 6 cows). Feeding behavior [the total time (min/d) that the animal spent with her head though the head-gate up to the withers, without being locked up in the head-gate for other reasons (e.g., for milking, for treatment, or for blood sampling)]; surgical site licking (licking of, or around the surgical site), and non-surgical site licking times were quantified continuously for 48 h following surgery. Tail flicking behavior was sampled as 0/1 during a 1 min continuous focal observation period every 20 min from 12:00 to 21:00 on d 0 and from 06:00 to 18:00 on day 1. The numbers of these events on days 0 and 1 were added and converted to a percentage based on the total of number of 1 min sampling intervals on each day (24 intervals for day 0 and 36 intervals for day 1). Total daily lying time and the number of transitions from standing to lying (or vice versa) were recorded using a 3-axis accelerometer [Hobo Pendant G loggers; Hoskin Scientific, British Columbia; (18)] attached to the right hind leg and recording at 1-minute intervals 7 d prior to surgery and 12 d post-surgery. Days started at 05:00 when each cow was forced to stand for milking. Total daily lying time (the sum of time spent lying both right and left from the raw data) and time spent lying on the left side were calculated from the data collected from this accelerometer using surgery completion time for each individual cow as time 0 for d 0, and d 1 started at 24 h post-surgery until 12 d after surgery. The data output from the accelerometer was manipulated as described in a previous study (18) for the 60 s sampling interval using a 1-event filter for potentially erroneous readings of lying or standing events.

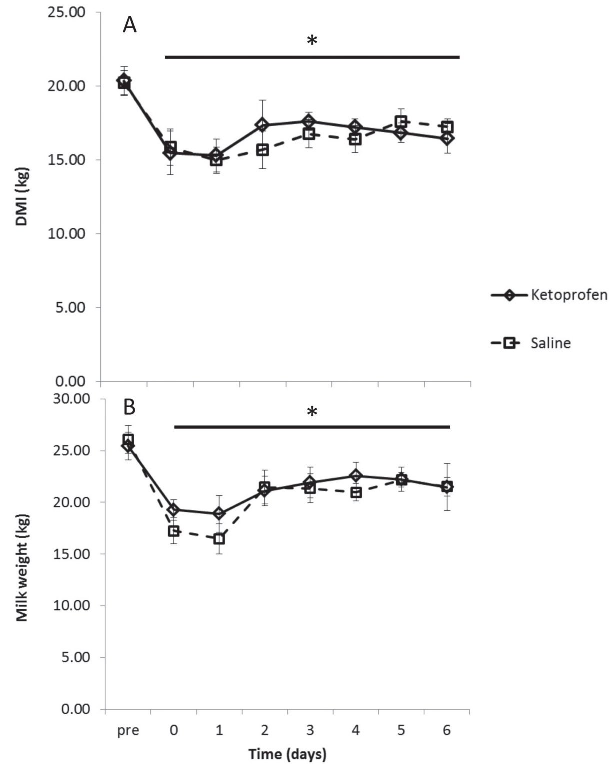

Figure 2. Daily average for (A) DMI (kg/d) (± SE) and (B) milk production (kg) (± SE) by treatment group around the first stage of fistulation surgery (laparotomy and clamp placement of the rumen) ($n = 18$). Pre-surgical average was the average for each outcome for 7 days pre-surgery, day 0 was the day of surgery and first treatment, and day 1 was the day post-surgery and second treatment. * indicates significant difference from pre-surgical average ($P < 0.05$).

Statistical analysis

All descriptive statistics, model building, and analyses were performed with STATA Intercooled 10.1 (StataCorp, College Station, Texas, USA). Mixed multivariable models were built and included a random intercept for animals to account for multiple measurements being taken from each cow. Mixed linear regression models were performed for the outcomes of DMI, milk production, lying behavior, physiological measurements (heart rate, respiration rate, rectal temperature, serum haptoglobin, and infrared temperature measurements around the surgical site) and for behaviors from video analysis. All tests were 2-sided and significance was based on $\alpha < 0.05$. For all models, time and treatment were forced in as covariate and were modeled as categorical variables. Each variable was pre-screened in a univariable model and kept in the final model if they were significant at $\alpha < 0.05$ level, acted as a confounder [defined as a non-intervening variable whose inclusion in the model made a 20% or greater change in the coefficient of significant variables in the final model (19)], or were part of a significant interaction term. Interactions between treatment and any significant covariates in the final model were tested. Two types of models were built for each outcome. The first set of models (Surgical Effect) was designed to test for the effects of the first stage of surgery on the outcome. Time was modeled as a categorical variable and pre-surgical values category was the referent. The models also controlled for treatment, and BW was forced in as covariate for the DMI and milk production models. The second set of models (Treatment Effect) was designed to test the effect of treatment administered on d 0 and d 1, and the time spent lying left model on days 0, 1, 7, and 8. As such, the time was included as a categorical variable for day 0 and 1 only, treatment was controlled for in the model and the pre-surgical average values (7 d prior to surgery for the DMI, milk production and lying behavior, and day 0 pre-surgical values for the other physiological measures) were included as a covariate in the models. For the infrared readings, the 4 reading positions were tested individually against the control position in order to determine which readings were significantly different from the control. Only the positions that were significantly different from the control position were averaged and used as the infrared reading outcome, and these included the bottom, right, and left readings around the surgical site.

The standardized residuals to identify outliers at the observation-level for the linear and mixed linear models were examined, and best linear unbiased predictors (BLUPS) for any outliers at the cow-level for the mixed linear models were determined. Normality and homogeneity of variance were assessed for the observation-level standardized residuals for mixed linear models, and BLUPS were examined. No problems were observed, and no transformations were required for any of the data sets.

Results

Effect of surgery

Following surgery there were significant decreases in DMI (Table 1; Figure 2A) and milk production (Table 1; Figure 2B) compared to pre-surgical averages. The respiration rate (RR) following surgery was not significantly different on day 1 compared to pre-surgical values on day 0 (Table 2). However, there were significant increases in the heart rate (HR), rectal temperature (RT), and infrared temperature (IRT) readings around the surgical site, and the serum haptoglobin concentrations following surgery on day 1 compared with the pre-surgical values on day 0 (Table 2). Serum haptoglobin peaked on day 3 (Table 2).

There were no differences in time spent at the feed bunk from day 0 to day 1 (Table 3). There was a significant decrease in surgical site licking, and a trend towards an increase in non-surgical site licking on day 1 compared with day 0 (Table 3). There was an increase in tail flicking behavior on day 1 compared to day 0 ($\beta = 3.5\%$; 95% CI: 1.7, 5.3; $P < 0.001$; Figure 3).

The total daily lying time did not change as a result of surgery or in response to treatment, with cows on average spending 12.3 h/d (± 2.7 SD) lying down. There was a decrease in the amount of lying time spent on the left side following surgery compared to the pre-surgical average (Table 1; Figure 4).

Effect of ketoprofen

Cows that were injected with ketoprofen tended to have increased milk production compared to cows that received saline on days 0 and 1 following surgery (Table 1; Figure 2B). There were no significant treatment effects for any of the physiological outcomes of HR, RR, RT, IRT, and haptoglobin concentrations (data not shown).

Table 2. Mean (± SE) for the heart rate (beats/min), respiration rate (breath/min), rectal temperature (°C), infrared temperature readings (°C) around the surgical site (average of the left, right, and bottom positions around the surgical site) and serum haptoglobin concentrations (g/L) before fistulation surgery on d 0 and after surgery by treatment group on days 1, 3, and 7, for 18 late lactation Holstein cows treated with either ketoprofen or saline on the day of surgery, and 24 h after surgery. Coefficient (β), 95% confidence interval (CI) and *P*-value for the Surgical Effect model for each outcome compared day 1 to day 0

	day 0	day 1	day 3	day 7	β (95% CI)	*P*-value
Heart rate (beats/min)	68.9 ± 2.2	75.1 ± 2.9	76.2 ± 3.4	74.9 ± 3.4	6.2 (2.4, 10.0)	0.01
Respiration rate (breaths/min)	28.0 ± 1.7	30.1 ± 2.1	34.4 ± 2.9	30.4 ± 2.2	2.1 (−0.77, 4.99)	0.15
Rectal temperature (°C)	38.2 ± 0.14	38.4 ± 0.13	38.5 ± 0.14	38.3 ± 0.13	0.20 (0.03, 0.36)	0.02
Infrared temperature (°C)	33.0 ± 0.46	35.8 ± 0.68	35.1 ± 0.46	34.8 ± 0.47	2.8 (1.8, 3.8)	< 0.001
Serum haptoglobin (g/L)	0.13 ± 0.03	0.30 ± 0.06	0.88 ± 0.09	0.87 ± 0.13	0.17 (0.09, 0.25)	< 0.001

Note: in each model, treatment and time as categorical variables were included, and pre-surgical values category was the referent for the time variable; SE — standard error.

Table 3. Observed mean (± SE), coefficient (β), 95% confidence interval (CI) and *P*-value for the surgical effect model for the time spent at the feed bunk (min/d), non-surgical site licking (min/d), and surgical site licking (min/d), expressed as a percent of total number of scans for each period, before fistulation surgery on day 0 and after surgery by treatment group on day 1, for 18 late lactation Holstein cows treated with either ketoprofen or saline on the day of surgery, and 24 h after surgery

	D 0	D 1	β (95% CI)	*P*-value
Time at feed bunk (min/d)	148.1 ± 28.6	156.2 ± 25.6	8.1 (−63.5, 79.6)	0.82
Non-surgical site licking (min/d)	0.47 ± 0.20	1.5 ± 0.90	1.0 (−0.10, 2.1)	0.07
Surgical site licking (min/d)	17.5 ± 2.6	8.9 ± 2.1	−8.5 (−14.5, −2.6)	0.01

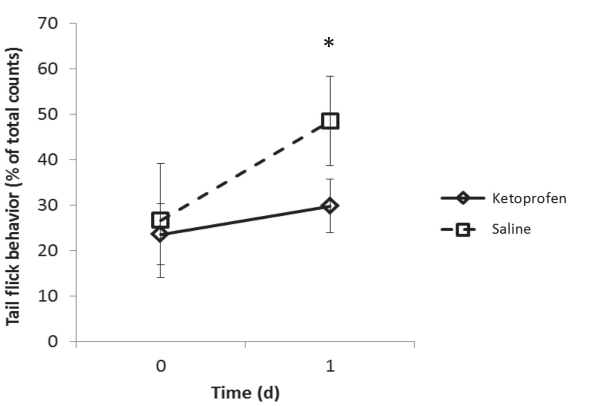

Figure 3. Tail flicking behavior expressed as a percent of total of counts during a 1-minute continuous focal observation period every 20 min on day 0 (from surgery completion to 21:00), and on day 1 (from 06:00 to 18:00), for 18 Holstein cows that underwent first-stage of a fistulation surgery. * indicates an increase in tail flicks from d 0 ($P < 0.05$), as well as a difference between treatment groups on day 1 ($P \leq 0.05$).

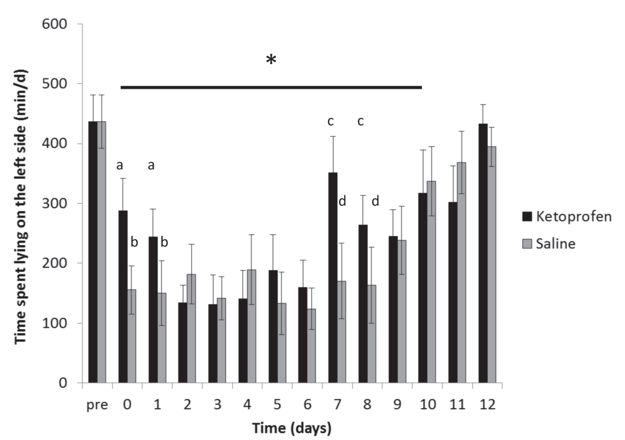

Figure 4. Average time spent lying on the left side (min/d) (± SE) by treatment group around the first and second stage of fistulation surgery (laparotomy and clamp placement of the rumen) ($n = 18$). Pre-surgical average was the average of the lying left time for 7 d pre-surgery, day 0 was the day of first stage surgery and first treatment, day 1 was the day post-surgery and second treatment, day 7 was the day of the second stage of surgery with treatment, and day 8 was the last day of treatment. * indicates significant difference from pre-surgical average ($P < 0.05$). The letters 'a' and 'b' indicate significant differences between treatment groups on days 0 and 1 ($P < 0.05$), and 'c' and 'd' indicate tendencies between treatment groups on days 7 and 8 ($P < 0.1$).

There were no differences in time spent at the feed bunk, non-surgical site licking, or surgical site licking between the 2 treatments. On day 1, saline-treated animals performed more tail flicking behavior compared to those that received ketoprofen (β = 5.8%; 95% CI: 1.5, 10.1; P = 0.01; Figure 3). Animals treated with ketoprofen spent significantly more time lying on their left side on days 0 and 1 post-surgery compared to animals treated with saline (Table 1, Figure 4), and there was a tendency for animals treated with ketoprofen to spend more time on their left side on days 7 and 8 compared with saline-treated animals (P = 0.07; Figure 4). It is noteworthy that on non-treatment days following either stage of the surgery (days 2 to 6 and 9 to 12) there were no differences between treatment groups, and that time spent lying on the left side on days 11 and 12 were not different compared with pre-surgical levels (Figure 4).

Discussion

Evidence presented herein clearly suggests that the first stage of the 2-stage rumen fistulation surgery resulted in pain as defined by the International Association for the Study of Pain (IASP) (20): an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Visceral pain in cattle is generally characterized by total or partial inappetence and increased heart rate (21) that were seen in this study.

Although pre-surgery serum haptoglobin values were within the reference range for healthy cows [i.e., ≤ 0.1 g/L; (22,23)], concentrations increased following fistulation, likely attributable to inflammation associated with tissue damage arising from surgery (24). The increase in IRT readings around the surgical site following surgery likely corresponded to inflammatory processes around the surgical site. The findings in the current study suggest further investigation is warranted on the IRT reading of the site of tissue trauma as a non-invasive method of assessing inflammation and pain. The small increase (0.2°C) in body temperature is difficult to explain and further research is needed to confirm this result.

Despite no changes in overall lying time associated with the surgery or drug treatment, the total time spent lying on the left side on the day of surgery and the days following surgery was much reduced compared with pre-surgical averages until day 11 when time spent lying on the left side started to return to pre-surgical levels. Most interesting, however, was that this latter observation was mitigated to some degree by the administration of ketoprofen.

This is the first study to describe the laterality of lying immediately following the first stage of rumen fistulation surgery. Unaltered cattle will typically spend approximately 50% of their daily lying time on the left side (25). Another study observed that left-sided ruminally cannulated animals spent less time lying on the left side compared to intact animals over a 48-hour observation period (26). This observation is consistent with the current work, in which cattle spent 55% of their lying time on the left side before surgery. This time was dramatically reduced to 31% in the days following the first stage of the fistulation procedure, suggesting that the reluctance to lie on the surgical side indicated post-surgical pain. This difference was only partly mitigated by ketoprofen (40%), perhaps because this NSAID has a plasma half-life of 2 h (27). The beneficial effects of ketoprofen following surgery appear to be inadequate at fully alleviating post-surgical pain on the days it was administered; as reflected by the result that post-surgical time spent on the left side did not return to pre-surgical levels. Furthermore, ketoprofen appeared to be beneficial only on the days it was administered, with its effect disappearing on non-treatment days following either stage of surgery. It may be useful for future studies to investigate different dosages of ketoprofen that may help achieve a good balance between mitigating pain, by using time spent lying on the surgical side as an indicator of pain, and preventing the cows lying on the surgical site in order to promote healing over the first 10 d following surgery. The findings from left-sided ruminally cannulated animals indicate that this pain may either continue in the months following the procedure, or that other aspects of cannulation have longer lasting effects on lying behavior and deserve future study (26).

In addition to lying position, other behavioral changes (e.g., tail flick behavior) are part of an overall integrated response to pain (28). In this study, the feeding times on day 1 were between 124 (saline group) and 187 (ketoprofen group) min/d, which is less than the 191 to 216 min/d previously reported for healthy cows (29). Perhaps the lower feeding time seen in this study can be attributed to post-surgical pain, and perhaps the non-significant drug effect on feeding time between treatment groups is due to the relatively short half-life of ketoprofen. In addition, due to the limited number of cows in this trial, perhaps the sample size was insufficient to detect differences associated with ketoprofen. The number of cows in this trial was determined by ethical considerations and calculations for the number of cows needed for the nutrition projects, and addition of further cows to this study was not possible.

The beneficial analgesic effects of ketoprofen following painful procedures, such as dehorning, have been investigated. For example, ketoprofen reduced head shaking and rubbing, ear flicks (30), and tail flicks (31,32) compared to control animals following hot-iron dehorning. The lower amount of tail flicking behavior on day 1 in ketoprofen-treated animals compared to animals that received saline may be an indicator that these NSAID-treated animals were in less pain. However, due to space restrictions at the research dairy, it was impossible to obtain a pre-surgical baseline for this behavior and further research is needed to confirm this phenomenon.

This study is one of the first to examine the use of an NSAID as a post-surgical pain management tool and provides a number of lines of evidence that fistulation surgery is indeed painful. Given that cows treated with ketoprofen tended to have higher milk production, spent more time lying on the side of the surgery on days 0 and 1, and had a lower number of tail flicks compared with those treated with saline it is clear these changes were likely due in part to the animals experiencing pain. The lack of treatment differences for the RR, HR, IRT, and haptoglobin concentrations on day 1 were likely due to the fact that the ketoprofen dosages administered in this study may not have been effective enough based on its relatively short half-life and perhaps also because these measurements were taken before the second injection at the time of blood sample collection. Future studies should investigate these parameters at closer intervals around treatment administration.

In the present study ketoprofen did not fully mitigate the negative consequences of the surgery on several measures and had no effect on others. Perhaps the minimal effect of ketoprofen post-operative pain in this study was due to the plasma half-life of 2 h and the elimination of 80% of the dose in the urine within 24 h of administration (27). In addition, we only provided ketoprofen on 2 occasions (24 h apart); it could be argued that the animals were possibly feeling pain between the first and second injections. Therefore, future research should investigate multiple daily injections of ketoprofen at the current label dose, or perhaps test a longer lasting NSAID.

This study is one of the first to examine the use of an NSAID as a post-surgical pain management tool in cattle. The results provide clear evidence that the first stage of a 2-stage fistulation surgery is painful and ketoprofen administered at a label dose of 3 mg/kg BW at the time of surgery, and 24 h following surgery, alleviated some, but not all, of the post-surgical pain. It is recommended that scientists include pain mitigation when performing rumen fistulation surgery in cattle used for research.

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