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Effects of nonsteroidal anti-inflammatory drugs, therapeutic hoof trimming, and orthopedic block application on lameness in multiparous dairy cattle: A randomized controlled trial

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ABSTRACT

Hoof horn lesions are recurrent in nature and cause long-term pathological challenges to the functional anatomy of the hoof in dairy cattle. It is hypothesized that inflammation is a driver of these pathological changes. It has previously been identified that routine treatment with nonsteroidal anti-inflammatory drugs (NSAID) at first and subsequent calving and lameness events is important in reducing the future risk of lameness in dairy heifers. The effects NSAID administration has on lameness outcomes for multiparous dairy cattle is unknown. We conducted a 34-mo randomized controlled trial to investigate the effects of routine administration of the NSAID ketoprofen during treatment for lameness and at calving on the future probability of lameness and culling caused by exposure to normal farm conditions. Dairy cattle that had calved at least once were recruited from a single herd and randomly allocated to 1 of 4 treatments controlling for parity, proportion of occasions scored as lame 8 wk before study onset, and DIM. All lactating animals were scored for lameness every 2 wk to identify lame animals requiring treatment. Animals in group 1 received a therapeutic trim and an orthopedic hoof block (if deemed necessary) every time they were treated for lameness. Animals in group 2 received a 3-d course of ketoprofen (single dose daily) alongside the same treatment given in group 1 every time they were treated for lameness. Animals in group 3 received a 3-d course of ketoprofen (single dose daily) starting 24 to 36 h after each calving alongside the same treatment given in group 2 for lameness. Animals in group 4 received a 3-d course of ketoprofen (single dose daily) every time they were identified with lameness, with no therapeutic trim, unless they were identified as severely lame (a single score ≥3a). Animals were followed for the 34-mo duration of the study. Independent lameness outcome scores were collected every 2 wk by technicians who were blinded to treatment group to assess the probability of lameness. Culling data were extracted from farm records. A total of 425 animals were recruited to the study (105 in group 1, 107 in group 2, 107 in group 3, and 106 in group 4), with data from 412 animals included in the final analysis (102 in group 1, 102 in group 2, 106 in group 3, and 102 in group 4). The effect of treatment group on the ongoing probability of lameness was evaluated through the use of mixed effect logistic regression models. Compared with animals in group 1, animals in group 4 were significantly more likely to be identified as lame throughout the study period. No effect on the risk of severe lameness was identified. The effect of group on time to culling was investigated using a Cox proportional hazards model. No benefit of the NSAID or hoof trimming intervention on culling risk was identified. Our results highlight the importance of frequent therapeutic trimming and the application of orthopedic blocks in the treatment of lameness in multiparous animals that may have a history of calving and lameness without NSAID administration.

Key words: dairy cow, NSAID, lameness, hoof horn lesion, hoof trimming

INTRODUCTION

Lameness is a condition that challenges the welfare of dairy cattle globally (von Keyserlingk et al., 2012; Ranjbar et al., 2016; Griffiths et al., 2018; Randall et al., 2019) and can reduce the profitability of a dairy enterprise (Huxley, 2013). Hoof horn lesions (**HHL**) have been identified to be a highly prevalent and recurrent cause of lameness throughout the global dairy herd (Leach et al., 2012; Solano et al., 2016). Lameness derived from HHL is a chronic condition, with long-term changes to anatomy being associated with their occurrence, including exostosis on the caudal aspect of the pedal bone, as described by Newsome et al. (2016), and a reduced digi-

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tal cushion volume, as described by Wilson et al. (2021). Randall et al. (2018) identified that previous lameness contributes substantially to the risk of future lameness. It has been hypothesized that changes to distal limb anatomy associated with HHL increase the animal's risk of lameness throughout its future life, including through exostosis of the pedal bone, as described by Newsome et al. (2016), and metabolism of the digital cushion, as described by Wilson et al. (2021, 2022).

Recent publications have discussed the potential importance of inflammation in the etiology of HHL (Newsome et al., 2016; Wilson et al., 2022; Wynands et al., 2022). Nonsteroidal anti-inflammatory drugs (**NSAID**), in combination with a therapeutic functional hoof trim and the application of an orthopedic block, have been shown to be useful for improving acute lameness cure rates (Thomas et al., 2015; Sadiq et al., 2022; Wilson et al., 2022) and pain modulation (Whay et al., 2005) but not the recovery of chronically lame cows (Whay et al., 2005; Thomas et al., 2016). Newsome et al. (2016) hypothesized that the development of exostosis on the most caudal aspect of the distal phalanx (associated with lameness) was partially driven by the inflammatory nature of HHL. Wilson et al. (2021) hypothesized that the HHL-associated inflammation can lead to adipose metabolism and remodeling in the digital cushion. Both of these pathological mechanisms may compromise the functionality of distal limb anatomy. Another key risk period challenging the structures within the hoof is calving (Tarlton et al., 2002; Wilson et al., 2022). Tarlton et al. (2002) identified changes to the suspensory apparatus associated with calving, which they hypothesized would increase the risk of HHL occurrence, and Wilson et al. (2022) identified that heifers receiving ketoprofen at first and subsequent calvings (alongside therapeutic trimming, orthopedic blocks, and ketoprofen at lameness events) experienced a reduced risk of lameness over 3 yr in a randomized controlled trial (**RCT**), highlighting the potential importance of transition-period inflammation in the etiology of HHL. Changes associated with calving and lameness are understood to increase the animal's risk of future lameness for the remainder of its life (Newsome et al., 2016; Wilson et al., 2021, 2022).

In a previous paper (Wilson et al., 2022), we identified that heifers routinely administered ketoprofen at first and subsequent calvings and during lameness treatment (alongside therapeutic hoof trimming and orthopedic block application) were at a significantly reduced risk of lameness or culling for the duration of the 34-mo study when compared with animals receiving no ketoprofen at calving or during lameness. It was postulated that inflammation associated with the transition period and lameness events was managed through the routine administration of NSAID at these time points. We hypothesized that the disease interventions may have minimized the risks of inflammation-driven anatomical changes to the distal phalanx and the digital cushion and hence reduced the risk of lameness in the future.

Research evidence on the use of NSAID as part of a treatment regimen for HHL is conflicting (Mason et al., 2022). In a study published by Laven et al. (2008) no benefit was identified from the routine administration of ketoprofen as part of HHL treatment. However, this may have been due to animals in that study being selected for treatment based on farmer identification of lameness. It has been shown previously that farmer identification of early-stage lameness is unlikely to occur (Leach et al., 2010; Ranjbar et al., 2020), suggesting that animals selected for this study may have had more severe and chronic HHL present. Within the cohort of animals described by Laven et al. (2008), pathological change to anatomy may already have occurred due to the stage of disease present. This could have nullified any positive effect of NSAID administration with respect to improving cure rates. Thomas et al. (2015, 2016) investigated the efficacy of therapeutic trimming, application of orthopedic blocks, and the administration of NSAID as lameness treatments. In those studies, it appears that chronically lame animals (with at least a 2-wk delay in treatment, which was often much longer in duration) had much poorer treatment outcomes (Thomas et al., 2016) than newly lame animals irrespective of the treatment regimen applied (Thomas et al., 2015). At present, there is little evidence to inform effective treatment interventions in dairy cattle that have a history of prior lameness.

The objectives of this study were to investigate the effects of long-term, routine treatment with NSAID at calving and during treatment for lameness on the future probability of lameness (primary objective) and culling (secondary objective) in multiparous dairy cows. Within the current study, a cohort of adult dairy cows, enrolled on January 8, 2019, were randomly allocated to 1 of 4 intervention groups to evaluate the effects of NSAID administration on the future probability of lameness and culling. Our primary null hypothesis stated that the strategic administration of NSAID at calving and lameness events would have no effect on the future probability of lameness in the study population. Our secondary null hypothesis stated that the strategic administration of NSAID at calving and lameness events would have no effect on the culling risk in the study population.

MATERIALS AND METHODS

Study Design

The current study was administered concurrently with the RCT described by Wilson et al. (2022), with all

lameness identification, treatment, and farm management protocols remaining the same. The only difference in protocol was in the study population recruitment and randomization process (in the current study, we enrolled animals on the first day of the study only, whereas in our previous study, we recruited continually as the trial progressed, i.e., a closed vs. an open population). We recommend readers to refer to Wilson et al. (2022) for a comprehensive description of the study methodology, which is briefly reviewed below.

The study was conducted in line with the REFLECT guidelines (O'Connor et al., 2010), to investigate the efficacy of long-term and routine administration of NSAID in the prevention and treatment of lameness. The University of Nottingham School of Veterinary Medicine and Science Ethics Committee granted ethical approval for the study to be conducted (reference no.: 1913 161208). The UK Veterinary Medicines Directorate granted approval for the NSAID ketoprofen to be used under an Animal Test Certificate Type S (reference no.: ATC-S-090). In the previously reported study (Wilson et al., 2022), the enrolled population comprised of a cohort of precalving dairy heifers, whereas in the current study, the enrolled population comprised lactating primiparous and multiparous dairy cattle that had calved at least once at the start of the study. The primary outcome measure of lameness state (defined by the lameness score) over time (repeated measures of lameness within cow) was used to assess our primary objective. Using a baseline proportion of 35% of animals identified as lame at least once during the study, in a 2-proportion sample size calculation, a group size of 102 animals would detect an absolute superiority margin of 18% in the primary outcome score (power = 0.8, type I error rate = 0.05). Given the repeat measures within cow (many lameness scores over time and multiple lactations per animal over the study period), this was a conservative estimate of the likely power in the final multilevel logistic regression analysis. The study aimed to enroll 102 animals per treatment group.

The additional outcome of time between study onset and culling was evaluated to assess our secondary objective.

Study Herd and Management

The single farm recruited for the current study was the same as that described in detail by Wilson et al. (2022). A brief summary of the herd management is described below.

The 490 milking cows in the herd on a farm in North Nottinghamshire, England, were milked through a rotary parlor 3 times daily, and the mean 305-d milk yield was ~11,600 L per cow. Animals were housed continuously in barns with rubber mattress stalls (bedded with sawdust and lime) and grooved concrete through the alleyways. Three housing barns were used to group the cows based on lactation stage (early, mid, or late lactation). A partial mixed ration was fed to milking cattle with additional concentrate in the parlor based on stage of lactation and yield (prepared in combination to maintain a peak lactational yield of 48 L/d).

Routine maintenance hoof checks were administered at each dry-off to each animal using the functional 5-step method described by Toussaint-Raven (1985) with a longer toe length being left (Archer et al., 2015) and a deeper, wider model (Stoddard, 2018; Sadiq et al., 2021) being taken than described in the original Toussaint-Raven method.

Enrollment and Retention

All cows that had calved at least once and not been marked to be culled within 6 mo of study initiation were enrolled in the trial on the January 8, 2018, regardless of lameness state. Animals were randomized to 1 of 4 treatment groups using the stratified randomization procedure described by Wilson et al. (2022). All animals that were in the milking herd (and thereby had calved at least once) underwent lameness scoring using the modified Agriculture and Horticulture Development Board lameness scoring system outlined by Thomas et al. (2015) every 2 wk ± 2 d for 8 wk before study onset (Table 1). Animals were grouped according to these scores: if an individual was identified as having a score of 2a or above at ≥50% of the prestudy scoring sessions, it was placed in group A; otherwise, the animal was placed in group B. This was carried out to ensure that lameness history was controlled for as a confounder, accounting for both historic challenge to distal limb anatomy and lameness presence at study onset. The randomization procedure was stratified as follows:

1. Animals were grouped by parity (1, 2, 3, or 4+).
2. The parity groups were subdivided into groups A and B by lameness scores.
3. Once the parity groups were subdivided according to lameness scores, animals were listed in order of their DIM at study onset.

This resulted in a list of animals in groups A and B for each of the 4 parity groups, with animals ordered by their DIM at study onset. Animals within these lists were then randomly allocated to 1 of the 4 treatments in the order in which they appeared on the list (i.e., they were grouped into fours based on calving date, and within that group of 4 animals, they were randomly allocated a treatment group between 1 and 4), using an online random block generator (Haahr, 2012). A single operator carried out

Table 1. Lameness scoring system[1] adapted from the scoring system described by Thomas et al. (2015)

Score	Description
0	Walks with even weight bearing and rhythm on all 4 feet, with a flat back. Long, fluid strides possible.
1	Steps uneven (rhythm or weight bearing or strides shortened, affected limb or limbs not immediately identifiable).
2a	Mild asymmetry in hind-limb movement. Decreased stride length of affected limb and slightly decreased stance duration with a corresponding increase in limb flight velocity on the nonaffected side. Walking velocity remains normal. Back may be raised.
2b	Moderate asymmetry in hind-limb movement. Decreased stride length of affected limb and a distinct decrease in stance duration. Limb flight of the nonaffected limb is correspondingly faster, and the overall walking velocity is reduced. Back usually raised.
3a	Severe asymmetry in hind-limb movement. Marked decrease in stride length of affected limb and very short stance duration. Limb flight of nonaffected limb rapid, and walking velocity reduced such that cow cannot keep up with healthy herd. Back raised.
3b	Minimal or no weight bearing on affected limb. Back raised. Reluctant to walk without encouragement.

[1]This scoring system was used in a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the subsequent risk of culling.

the enrollment, randomization, and group allocation processes (J. P. W.).

Animals remained in the study until the end date or culling. Animals were excluded from the study if at any time they posed a danger to the technicians administrating the study or to themselves.

Lameness Identification and Treatment

To identify individuals that would benefit from treatment, lameness scoring was conducted as described by Wilson et al. (2022), and scores are shown in Table 1. Lameness scoring, treatment, and all associated tasks (e.g., assessment of agreeability between observers) conducted as part of the study occurred concurrently with and followed the same protocol as the previously described study. The 3 operators carrying out lameness treatment underwent the same auditing processes and followed the same trimming, lesion identification, and treatment protocols. Technicians administering lameness treatments were partially blinded to treatment group, with the treatment group being revealed once the therapeutic trim and orthopedic block had been applied to animals in groups 1, 2, and 3. Hoof blocks were applied to any hoof with a HHL, provided that no response was elicited by a hoof tester on the partner digit to the diseased digit or that the cow did not have a thin sole on the partner digit to the diseased digit.

Farm staff were blind to the study and treatment protocols but did assist with study implementation. Animals were treated according to their treatment group for the entirety of the study, according to the same protocol as previously described. Animals would be treated and then enter a 28-d refractory period posttreatment to allow time for recovery; after this refractory window had passed, they would become eligible to be treated again.

Treatment Groups

The RCT was designed to establish the efficacy of 4 different approaches to the prevention and treatment of lameness in cattle that had calved at least once in their lifetime. The same treatment protocols as used by Wilson et al. (2022) were followed and are described in Table 2.

Lameness Outcome Scores

Animals in the study underwent lameness scoring at an interval of 2 wk (± 2 d) by 1 of 2 trained, independent lameness scorers who were blinded to treatment group

Table 2. Treatment regimens applied in a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the subsequent risk of culling

Treatment group[1]	Trim when identified as lame	NSAID (3-d course) when identified as lame	NSAID (3-d course) at every calving event
1	Yes	No	No
2	Yes	Yes	No
3	Yes	Yes	Yes
4	No (unless severely lame)	Yes	No

[1]Animals allocated to treatment group 1 received a therapeutic trim and orthopedic block when identified as lame (lameness score ≥2a) during routine lameness scoring conducted at a 14-d interval. Animals allocated to treatment group 2 received a therapeutic trim and orthopedic block when identified as lame and a 3-d course of the NSAID ketoprofen. Animals allocated to treatment group 3 received a therapeutic trim, orthopedic block, and 3-d course of ketoprofen when identified as lame, as well as a 3-d course of ketoprofen at each calving event that occurred throughout the study. Animals allocated to treatment group 4 would only receive a 3-d course of ketoprofen when identified as lame, unless identified as severely lame (lameness score ≥3a), in which case they would be eligible to receive a therapeutic trim and an orthopedic block.

to generate a blinded outcome measure, as described by Wilson et al. (2022). The technicians played no other role in study administration or management.

Data Collection and Descriptive Analysis

A relational database (Microsoft Access, Microsoft Corp., 2016) was used to collate and store data every 14 d (± 2 d). Lameness occurrence was the primary outcome of interest (determined through routine blinded lameness scoring), and time from study onset to herd exit (defined by on farm records of death or culling) was the secondary outcome. A binary outcome was defined for lameness for each 2-wk score; if the lameness score was ≥2a, the cow would be defined as lame, and if the lameness score was <2a, the cow would be defined as not lame. A similar approach was used to define severe lameness, where a threshold of ≥3a was applied to the binary outcome. The days elapsed between the onset of the study and the day of death (as recorded by farm staff) defined the outcome of time to culling (irrespective of the nature of death, i.e., voluntary culling or dispatch on farm). The primary reason for culling was determined from farm records. Weeks in the study was defined as the number of weeks that passed between the study start date and when slaughter or death occurred or when the trial ended (exiting the study).

These outcome scores were determined and managed independently from the lameness scores identifying animals for treatment (i.e., animals would not be selected for treatment from the blinded lameness outcome score). The treatment and outcome score databases were managed separately from each other to ensure that blinding was maintained among the technicians administering the study. Microsoft Excel 2016 (Microsoft Corp., 2016) and R V4.0.3 (R Core Team, 2020; https://www.R-project.org/) were used for data handling and analysis. Calving dates, lameness scores, treatment groups, weeks in the study, and culling dates were all collated. Anomalous or missing data were identified through initial data handling and screening. If anomalous data were identified before inclusion or exclusion, the source of the error was reviewed to determine the validity of the data before deciding whether it should be removed.

Statistical Modeling

Three statistical models were constructed to evaluate the study hypotheses using a forward-stepwise approach. To evaluate the effects on the time-dependent probability of lameness (as identified by a blinded lameness outcome score ≥2a) or severe lameness (as identified by a blinded lameness outcome score ≥3a), 2 mixed effects logistic regression models were constructed using the lme4 (Bates et al., 2015) package in R (model A and model B). The mixed effects logistic regression models took the following form:

$$\text{Lameness}_{ij}\ (1 = \text{lame}, 0 = \text{not lame}) \sim \text{Bernoulli}\ (\mu_{ij})$$

$$logit(\mu_{ij}) = \beta_0 + \beta_1 \mathbf{x}_{ij} + \beta_2 \mathbf{x}_j + u_j$$

$$u_j \sim N(0, \sigma^2),$$

where μ_{ij} is the probability of an animal being lame or severely lame at the ith scoring of the jth cow, β_0 is the model intercept, $\mathbf{x}_{ij}$ is a matrix of covariates linked to each lameness score (DIM at outcome assessment or weeks in study, both of which were tested as $\log_{10}$ polynomial terms in the models to a power of 4), β_1 is the coefficient for $\mathbf{x}_{ij}$, $\mathbf{x}_j$ is a matrix of covariates linked to each cow (i.e., treatment group), β_2 is the coefficient for $\mathbf{x}_j$, u_j represents a random effect (random intercept) for the jth cow to account for repeated measures within cow, and σ^2 is the variance of the random effect u_j.

Covariates remained in the model and were deemed significant when $P < 0.05$. Interactions between significant covariates were tested, and covariates were retained in the model when $P < 0.05$. Treatment group and weeks in study were forced into the final models as covariates required to test our hypothesis. Model fit was investigated by assessing realized discrepancies between observed outcomes and cumulated predicted probabilities (Gelman et al., 1996) and evaluating the normality of random effects (through a Q-Q plot). As random effects were over dispersed, the final models were repeated to omit outlying cows (>10 occurrences of lameness during the study period) to ensure no consequential changes in model parameters or their interpretation. Graphical visualizations were created of the final models to illustrate them by treatment group and the probability of lameness or severe lameness for the duration of the study. A random effect for cow was included to account for repeated measures of lameness over time within each individual. The binary variable previously described in the randomization process accounting for lameness history (group A or B) was also forced into the model as a covariate to test for potential confounding.

To investigate the effect of treatment group on time to culling, a Cox proportional hazards survival model was constructed using the survival (Therneau and Grambsch, 2000) and survminer (Kassambara et al., 2020) packages in R (model C). The Cox proportional hazards model took the following form:

$$h(t) = h_0(t) \times \exp(\beta_1 x_1 \ldots \beta_p x_p),$$

where t represents the survival time to culling, and $h(t)$ is the hazard function that is dependent on a baseline

hazard $h_0(t)$ and p covariates ($x_1 \ldots x_p$) with the related coefficients $\beta_1 \ldots \beta_p$.

Covariates were retained in the Cox proportional hazards model and deemed significant when $P < 0.05$. Days in milk and parity were tested as covariates. The proportional hazard's assumption and model fit were evaluated through visual evaluation of Schoenfeld residuals, the log-log curves, and delta betas (Schoenfeld, 1982; Grambsch and Therneau, 1994) The data were visualized graphically to illustrate time to culling by treatment group using Kaplan-Meier plots.

RESULTS

Study Denominators

In total, 425 animals were randomized into the 4 treatment groups after initial selection, with 105 in group 1, 107 in group 2, 107 in group 3, and 106 in group 4 present for lameness scoring (i.e., they were not culled between randomization taking place and being eligible to be scored). Subsequently, 13 cows (3 from group 1, 5 from group 2, 1 from group 3, and 4 from group 4) posed a danger to the study technicians during implementation of the protocol and were removed from the study. The reasons for these exits were considered to not be linked to treatment group (i.e., they occurred at random). For the final analysis, 102 animals in group 1, 102 in group 2, 106 in group 3, and 102 in group 4 were included, resulting in a total of 412 animals in the final dataset.

During study administration and routine veterinary attendance to the farm, no adverse events were associated with the administration of the treatment protocol across any of the treatment groups.

Descriptive Statistics

A total of 2,028 lameness treatments were administered to study animals (506 under group 1 protocols, 417 under group 2, 529 under group 3, and 576 under group 4) over the duration of the study. During the study, 238 cases of lameness were recorded as being associated with infectious causes (e.g., digital dermatitis), 1,422 were associated with HHL (primarily white line disease, sole ulceration, and sole hemorrhage), and 7 were derived from other causes (e.g., musculoskeletal injury). No visible HHL or infectious lesion was present in 361 cases of lameness, and the cause of the mobility challenge was unknown. Blinded outcome lameness scores were collated for the full study period duration (34 mo), yielding 14,021 individual lameness scores. Table 3 provides summarized data on the administered treatments and outcome lameness scores.

A total of 345 study animals were culled during the study (84 from group 1, 84 from group 2, 89 from group 3, and 88 from group 4). Farm records describing primary reasons for culling included fertility (n = 94), lameness (n = 30), udder health (n = 156), other (n = 38), and no recorded reason (n = 27). Table 4 provides a summary of culling data by treatment group.

Statistical Modeling

Model A. Model A was a mixed effects logistic regression model evaluating the effect of treatment group on the probability of lameness (score ≥2a, Figure 1).

Table 5 provides the final results of model A, with group 1 as the baseline for ease of comparison. Compared with cows in group 1, cows in group 4 were more

Table 3. Descriptive statistics of lameness data[1]

Item	Group 1	Group 2	Group 3	Group 4
Number of animals per treatment group included in final analysis	102	102	106	102
Proportion of outcome lameness scores recorded as lame	1,633/3,587 (45.5%)	1,500/3,421 (43.8%)	1,586/3,546 (44.7%)	1,726/3,467 (49.7%)
Proportion of outcome lameness scores recorded as severely lame	138/3,587 (3.9%)	99/3,421 (2.9%)	154/3,546 (4.3%)	147/3,467 (4.2%)
Number of lameness treatments administered	506	417	529	576
Number of animals that did not receive a lameness treatment	28	31	42	26
Mean (range) lameness treatments administered per animal	4.52 (0–18)	4.01 (0–20)	4.56 (0–19)	5.38 (0–20)
Number of hoof blocks applied	197	174	233	46
Number of additional first aid lameness treatments required	15	8	12	13
Number of veterinary referrals for lameness	10	8	4	15
Number of animals requiring more than one lameness treatment	53	46	34	60

[1]In this 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the subsequent probability of culling, 14,021 individual lameness scores were collected from 412 animals. Animals were enrolled and the study began on January 8, 2019. Treatments at lameness events and calving were administered according to the treatment group to which the animal belonged. The number of treatments administered does not include the number of "calving treatments" administered in treatment group 3. Animals requiring a first aid intervention were identified as having a score ≥3a outside of the regular treatment routines (i.e., outside of the regular 14-d lameness score). Animals would require a veterinary referral if they had lesions with a secondary infection or lesions that required surgery or local anesthesia to treat.

Table 4. Descriptive statistics of reason for culling[1]

	Culling reason				
Group	Udder health	Fertility	Lameness	Other	No recorded reason
1	34	23	9	11	7
2	41	21	6	8	8
3	40	24	5	10	10
4	41	26	10	9	2

[1]Data are derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the subsequent risk of culling.

likely to become lame during the study (odds ratio [**OR**] = 1.68, 95% CI: 1.29–2.07, $P = 0.01$). No statistical difference was observed between cows in group 1 and cows in groups 2 (OR = 1.05, 95% CI: 0.66–1.44, $P = 0.81$) or 3 (OR = 1.03, 95% CI: 0.64–1.42, $P = 0.89$). Days in milk and lameness category at randomization were tested as covariates and were removed from the final model as they had no effect on the outcome. Omission of outlying cows did not affect model parameters (<5% alteration in coefficients and no changes in significance); thus, they remained in the model, and model fit was deemed to be good.

Model B. Model B was a mixed effects logistic regression model evaluating the effect of treatment group on the probability of severe lameness (score ≥3a).

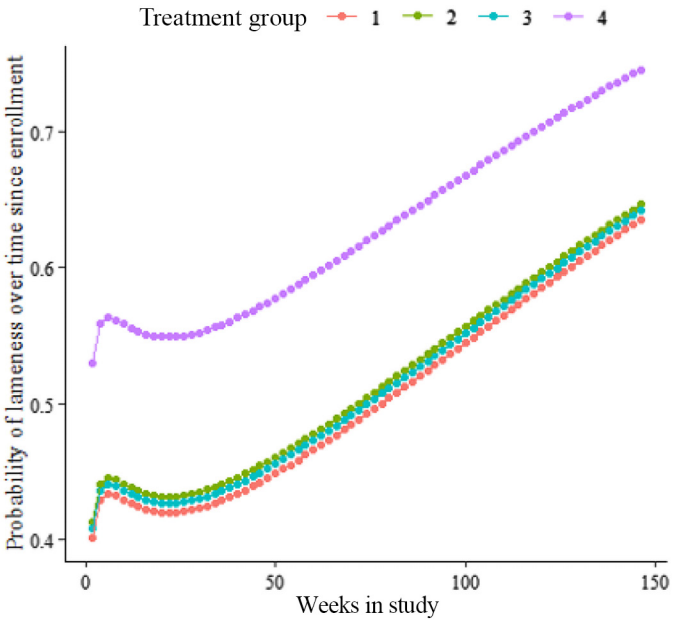

Figure 1. Graphical representation of predictions from the mixed effects logistic regression model investigating the effect of treatment group on the probability of lameness (lameness score ≥2a). These data are sourced from a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness. The dataset contained 14,021 individual lameness scores from 412 animals over the duration of the study.

Table 6 provides the final results of model B, with group 1 as the baseline for ease of comparison. No statistically significant effect was observed between the treatment groups on the risk of an animal being scored as severely lame ($P > 0.05$). Days in milk and lameness category at randomization were tested as covariates and were removed from the final model as they had no effect on the outcome. As for model A, the fit was good for model B. Outliers were tested and had no effect on model parameters; thus, they remained in the final dataset.

Model C. Model C was a Cox proportional hazards model evaluating the effect of treatment group on survival to culling.

Table 7 provides the final results of model C. No statistically significant effect was observed between the treatment groups on the risk of an animal being culled at any point of the study period. Parity and DIM were not included as covariates in the final model. Figure 2 illustrates the survival time to culling by treatment group through a Kaplan-Meier plot. Treatment group was forced into the model as the primary covariate of interest. The model assumption of proportionality of hazards was met, and residual analysis indicated the fit was good.

DISCUSSION

Our study was unable to identify a benefit from the routine administration of NSAID in respect to future lameness risk or culling. The current study was designed as a superiority study, meaning that our results were inconclusive as to whether NSAID administration was beneficial for the outcome measures studied in the current population. A potential smaller effect size of NSAID use may have been present; however, our study sample size was not adequate to detect this.

This study, when considered in combination with our previous study (Wilson et al., 2022), which investigated the use of the same treatments in primiparous heifers, highlights the importance of NSAID usage during lameness and the transition period in heifers that are calving for the first time. In our previous study (Wilson et al., 2022), we identified that animals receiving NSAID at

Table 5. Output from a mixed effects logistic regression model investigating the effect of treatment group on the ongoing probability of lameness (lameness score ≥2a)[1]

Item	Estimate	Odds ratio	SE	*P*-value
Intercept	−1.26	0.28	0.49	0.01
Treatment group 1	Reference			
Treatment group 2	0.05	1.05 (95% CI: 0.66–1.44)	0.20	0.81
Treatment group 3	0.03	1.03 (95% CI: 0.64–1.42)	0.20	0.89
Treatment group 4	0.52	1.68 (95% CI: 1.29–2.07)	0.20	0.01

[1]Data are from a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness. The analyzed dataset contains 14,021 individual lameness scores from 412 animals. The risk of lameness over time was controlled for by including weeks in study (logged to base 10) and polynomial terms for logged weeks in study (to power 3) in this final model. The study began on January 8, 2019, and the treatment groups represent 4 different treatment regimens administered at calving and lameness events.

first and subsequent calvings, as well as lameness events, were at a significantly reduced risk of being culled or identified as lame throughout the 34-mo study period. The findings of the current study, which enrolled multiparous animals with a limited lameness history, did not identify a benefit associated with the administration of NSAID at lameness events or calving in animals that had calved at least once. The results of both studies combined suggest that to deliver benefits regarding long-term lameness or culling, the group 3 protocol needs to take place in heifers calving for the first time and carried forward for the remainder of their productive lives. Based on the results of this study, the group 3 protocol of administering NSAID at calving and lameness events does not appear to be a suitable long-term lameness prevention regimen for multiparous dairy cattle. From a welfare perspective, however, it should be noted that we still recommend the routine use of pain relief for any animal experiencing a painful event (e.g., calving and lameness). It is important to note that we do not wish to diminish the importance of pain management when treating lame animals. In the current study, we did not measure any form of transient pain relief derived from NSAID usage; thus, a short-term effect may have been imparted but not identified due to the outcome measures of the study. This short-term transient benefit requires further research to elucidate.

The factors influencing the efficacy of NSAID administration at calving and lameness events in this current study are unknown, but several hypotheses are possible. We hypothesize that the animals in the current study had undergone a degree of pathological change to the functional anatomy of the hoof, as described by Newsome et al. (2016) and Wilson et al. (2021). This pathological change would likely mean that these animals were already at an increased risk of lameness before the beginning of the study, which would not be altered by NSAID administration (as NSAID administration is unlikely to reverse pathological changes to anatomy that have occurred previously). This increased risk of lameness due to pathological changes to anatomy could effectively render any potential NSAID administration at future inflammatory events ineffective with respect to minimizing the risk of future lameness events.

The findings of our study do present a challenge to managing lameness on farm in that NSAID administration at these time points may not present a substantial benefit to managing animals that have already calved into the herd. However, it appears that therapeutic trimming and the application of orthopedic blocks were more important than NSAID administration in relation to lameness in this group of cattle. Animals only receiving NSAID during lameness treatment (group 4) exhibited

Table 6. Output from a mixed effects logistic regression model investigating the effect of treatment group on the ongoing probability of severe lameness (lameness score ≥3a)[1]

Item	Estimate	Odds ratio	SE	*P*-value
Intercept	−1.93	0.15	1.15	0.10
Treatment group 1	Reference			
Treatment group 2	−0.25	0.77 (95% CI: 0.05–1.49)	0.37	0.49
Treatment group 3	0.16	1.17 (95% CI: 0.46–1.88)	0.36	0.65
Treatment group 4	0.28	1.32 (95% CI: 0.61–2.03)	0.36	0.43

[1]Data are from a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness. The analyzed dataset contains 14,021 individual lameness scores from 412 animals. The risk of lameness over time was controlled for by including weeks in study (logged to base 10) and polynomial terms for logged weeks in study (to power 3) in this final model. The SE corresponds to the odds ratio. The study began on January 8, 2019, and the treatment groups represent 4 different treatment regimens administered at calving and lameness events.

Table 7. Results of a Cox proportional hazards model for time to culling[1]

Model term	Coefficient	Hazard ratio	*P*-value
Treatment group 1	Baseline	—	—
Treatment group 2	−0.08	0.92 (95% CI: 0.68–1.23)	0.63
Treatment group 3	0.17	1.19 (95% CI: 0.87–1.61)	0.28
Treatment group 4	0.08	1.08 (95% CI: 0.80–1.48)	0.61

[1]Data used to construct this model originate from a 34-mo-long randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the risk of culling. The model contains data from 412 animals sourced from a single commercial herd. During the study period, 345 animals were culled. The study began on January 8, 2019, and the treatment groups represent 4 different treatment regimens administered at lameness and calving events.

a significantly increased risk of being scored as lame throughout the study period compared with animals that received a trim and block when treated for lameness (group 1). We hypothesize that through the application of a block and therapeutic trim that static and dynamic forces were alleviated from regions where pathological change had occurred. This alleviation of pressure could reduce the traumatic effects of new bone growth, even when the functionality of the digital cushion has been compromised, on sole soft tissues. This reduction of trauma to the sole soft tissues would in turn reduce the risk of lameness within the affected hoof. Implementing a high maintenance category for animals on farm wherein they proactively receive shorter-interval functional trims and orthopedic blocks where required may minimize the risk of lameness in the future. This would likely be beneficial for animals with a more severe history of lameness where there is a high likelihood of substantial pathological change challenging the animal's ability to walk comfortably for the rest of their lives. At present, we feel that implementing checks at an interval of 60 to 80 d in these animals would garner benefit, provided that a high-sensitivity fortnightly mobility score is also in place. The application of functional, routine hoof trimming in animals that have experienced lesions or lameness requires further investigation. We would emphasize that hoof trimming techniques should be better investigated specifically in animals with a history of lameness, alongside the timing of intervention, to understand its efficacy in reducing load bearing from areas affected by pathological change in order to reduce the future risk of lameness and lesions occurring. The choice of orthopedic block (regarding dimensions and material, e.g., rubber or wood) and application method also requires further investigation as to the optimization of protocol to reduce the risk of HHL occurrence to the blocked digit.

We advocate for farm staff, veterinarians, and hoof trimmers to implement more regular mobility checks, with fortnightly mobility scoring being a key recommendation. Animals should receive a hoof check each time they are ascribed a lame score (unless they are already undergoing treatment), with a block being applied whenever a lesion is identifiable (or a hoof tester elicits a withdrawal response), provided that the partner digit does not

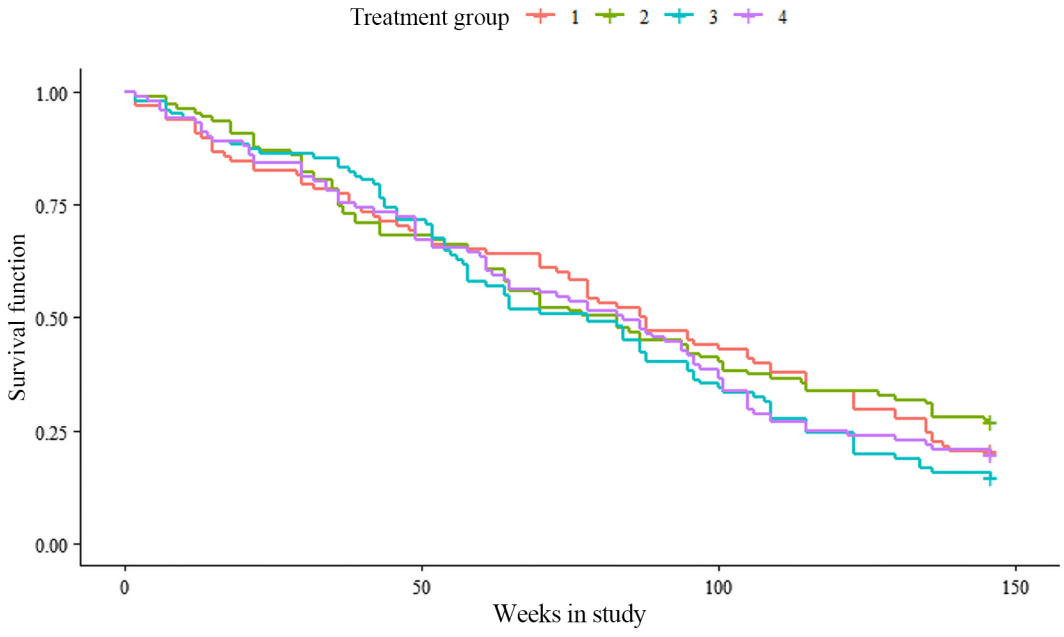

Figure 2. Kaplan-Meier plot for the survival analysis of multiparous cows subjected to 1 of 4 lameness treatment protocols over a 34-mo-long randomized controlled trial. The trial investigated the efficacy of nonsteroidal anti-inflammatory drugs in the prevention and treatment of lameness and the risk of culling.

exhibit a response to the hoof tester and is in a healthy condition. By further monitoring these individuals with a fortnightly mobility score, intervention with therapeutic trimming, and orthopedic blocks can be used to promote improved mobility. We hypothesize that some recent innovations in block technology would improve animal outcomes further; however, we recognize that block selection with respect to lameness cure rates and improving animal mobility while under treatment requires further research. The use of these blocking modalities may help to reduce the risk of future lameness until the point at which the animal is culled (which should be prioritized if chronic mobility challenge is present). In the studies described by Newsome et al. (2016) and Wilson et al. (2021), the majority of animals showed more pathological change on their lateral digits than their medial digits in the hind limbs. This suggests that with good block application procedures and monitoring, this healthier medial digit anatomy could be used to support improved mobility when lesions are present on the lateral digits of the hind limbs.

Our results may explain some of the findings of a recent systematic review of the literature investigating the usage of NSAID in the management of lameness (Mason et al., 2022). Mason et al. (2022) identified that several studies investigating the usage of NSAID in lameness management (O'Callaghan-Lowe et al., 2004; Whay et al., 2005; Laven et al., 2008; Thomas et al., 2015, 2016; Miguel-Pacheco et al., 2016) did not provide conclusive evidence to support their usage in improving cure rates or reducing animal behaviors associated with pain. Based on the results from the current study and our previous study (Wilson et al., 2022), we hypothesize that the papers critiqued by Mason et al. (2022) did not identify a significant benefit from NSAID usage because they did not control for lameness history within the study population. When making comparisons between the current study and our study investigating the population of heifers (Wilson et al., 2022), the only difference in study design is the population recruited, with the population of heifers studied by Wilson et al. (2022) having a lower chance of experiencing lameness previously (Offer et al., 2000; Randall et al., 2018). The heifers previously investigated had a low chance of pathological change occurring within the hoof capsule (due to a low risk of previous HHL occurrence before first calving). The cattle in the current study may have a history of lameness (indeed, it is likely that many of the multiparous animals had experienced lameness previously), meaning that pathological change to anatomy was likely to be present. We hypothesize that the difference in pathological changes between heifers and adult dairy cattle nullified the effects of NSAID administration, as observed in the current study. This mechanism could apply to the papers described by Thomas et al. (2015, 2016), in which chronically lame animals had a reduced chance of a cure in 5 wk compared with that of newly lame animals. This finding, in line with the current study's findings, highlights the importance of participant selection dependent upon the research question; for example, using animals with a low risk of lameness history, or controlling more substantially for lameness history, in future research to identify interventions that could reduce the risk of recurrently lame animals. Without this differentiation, there is a risk that utilizing these 2 distinct populations as 1 group in a study may mean that animals with pathological change to distal limb anatomy (derived from previous lameness) could mask any identifiable benefit to those without a history of lameness. We would encourage readers to view these populations as 2 distinct groups of study animals in the future.

Of equal importance is understanding how to manage animals with pathological change present within the hoof capsule, which still requires further investigation based on this defined population. The substantially larger proportion of the study population being identified as lame in the current study than in our previous study highlights the need for better understanding of the long-term prognosis for animals experiencing lameness after the defined treatment period when a clinical resolution can be achieved (if indeed it ever can be successful with pathological change that has already occurred to the anatomy of the hoof).

Regarding the presence of pathological change to distal limb anatomy, a history of unmanaged inflammation at lameness events may affect the animal's nociceptive threshold. It has been reported that animals experiencing severe lameness also have an increased expression of inflammation in the central nervous system (Herzberg et al., 2020), which could lower their nociceptive threshold or lead to a state of chronic pain. Furthermore, if pathological change to the soft tissues or pedal bone in the hoof capsule (as described by Wilson et al. (2022) and Newsome et al. (2016), respectively) has taken place, then there is a risk that the animal may experience pain purely due to the presence of dysfunctional anatomical structures. Further investigation into the pathophysiology, prevention, and management of pain associated with a case of lameness is warranted to understand how we can better mitigate the risk of an animal entering a state of chronic pain or having a lower nociceptive threshold.

Further research is required to understand the generalizability of our studies across a range of dairy systems, as a limitation of them is that they were only conducted on a single farm. The reasonings behind culling decisions on farm are complex. Animals in this unit that experienced chronic disease could be more likely to remain in the herd for reasons such as higher milk yield, for example.

This could nullify the effects of treatments, meaning that the effect size of an intervention would need to be large to be observable. Understanding how to manage animals that may be experiencing chronic conditions is important, and the authors would advocate this population being the subject of future research pertaining to their management.

In conclusion, we did not identify any benefit from NSAID administration at calving and lameness events in multiparous cows who may have experienced lameness previously with respect to the future risk of lameness and culling. The authors, however, do not wish to diminish the importance of pain relief for multiparous dairy cattle experiencing painful events and would promote the use of high-maintenance, proactive, functional trim lists, wherein animals with a history of lameness receive more regular functional trimming throughout a lactation. Furthermore, we would advocate more regular mobility scoring, alongside the use of functional hoof trimming and orthopedic block applications, in animals that may have a lameness history to reduce their risk of future lameness.

NOTES

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Nonstandard abbreviations used: HHL = hoof horn lesion; NSAID = nonsteroidal anti-inflammatory drugs; OR = odds ratio; RCT = randomized controlled trial.

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