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# Effects of routine treatment with nonsteroidal anti-inflammatory drugs at calving and when lame on the future probability of lameness and culling in dairy cows: A randomized controlled trial

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## ABSTRACT

Claw horn lesions (CHL) are reported as the most common cause of lameness in intensive dairy systems. Despite their prevalence, the underlying pathological mechanisms and preventive strategies for CHL remain poorly understood. Recent advances have pointed to the role of inflammation in disease aetiopathogenesis. Moderating inflammation from first calving may lead to long-term benefits and a viable intervention for treating and preventing disease. We conducted a 34-mo randomized controlled trial to investigate the effects of routine treatment with the nonsteroidal anti-inflammatory drug ketoprofen at calving and during treatment for lameness, on the future probability of lameness and culling, caused by exposure to normal farm conditions. A cohort of dairy heifers were recruited from a single, commercial dairy herd between January 8, 2018, and June 22, 2020, and randomly allocated to one of 4 treatment groups before first calving. The lactating herd was lameness scored every 2 wk on a 0 to 3 scale, to identify animals that became lame (single score ≥2a) and hence required treatment. Animals in group 1 received a therapeutic trim and a hoof block on the sound claw (if deemed necessary) every time they were treated for lameness. Animals in group 2 received the same treatment as group 1 with the addition of a 3-d course of ketoprofen (single dose daily) every time they were treated for lameness. Animals in group 3 received the same treatment as group 2 with the addition of a 3-d course of ketoprofen (single dose daily) starting 24 to 36 h after each calving. Animals in group 4 received a 3-d course of ketoprofen (single dose daily) every time they were identified with lameness. No therapeutic trim was administered to this group, unless they were identified as severely lame (a single score ≥3a). Animals were followed for the duration of the study (ending October 23, 2020). Probability of lameness was assessed by a lameness outcome score collected every 14 d. Data on culling was extracted from farm records. One hundred thirty-two animals were recruited to each group, with data from 438 animals included in the final analysis (111 in group 1, 117 in group 2, 100 in group 3, and 110 in group 4). Mixed effect logistic regression models were used to evaluate the effect of treatment group on the ongoing probability of lameness. Compared with the control group (group 1), animals in group 3 were less likely to become lame (odds ratio: 0.66) and severely lame (odds ratio: 0.28). A Cox proportional hazards survival model was used to investigate the effect of treatment group on time to culling. Compared with group 1, animals in groups 2 and 3 were at reduced risk of culling (hazard ratios: 0.55 and 0.56, respectively). The lameness effect size we identified was large and indicated that treating a cohort of animals with the group 3 protocol, would lead to an absolute reduction in population lameness prevalence of approximately 10% and severe lameness prevalence of 3%, compared with animals treated in accordance with conventional best practice (group 1).

**Key words:** dairy cow, nonsteroidal anti-inflammatory drug, lameness, claw horn lesion, calving

## INTRODUCTION

Lameness presents a substantial challenge to the sustainability of the dairy industry. It causes financial losses through depression of milk production, reduced reproductive efficiency, and increased culling risk (Huxley, 2013), and greatly affects cow welfare (Whay and Shearer, 2017). Because the current mean prevalence of lameness is estimated at ~30% in the United Kingdom (Griffiths et al., 2018; Randall et al., 2019), between 22 and 55% in the United States (Cook, 2003; Espejo et

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al., 2006; Von Keyserlingk et al., 2012), and ~19% in Australia (Ranjbar et al., 2016), a substantial reduction in lameness remains a key goal for the global dairy industry.

The causes of lameness can broadly be categorized into infectious conditions (such as digital dermatitis and interdigital necrobacillosis) and the claw horn lesions (**CHL**). Claw horn lesions primarily include sole hemorrhage (**SH**), sole ulceration (**SU**), and white line disease (**WLD**), which are reported to be the most common cause of lameness in intensive dairy systems (Leach et al., 2012; Solano et al., 2016).

The underlying pathological mechanisms and risk factors for CHL are not well understood (Randall et al., 2018b). Mechanisms reported to increase the risk of CHL include local inflammatory events within the hoof (Newsome et al., 2017), weakening of the suspensory apparatus attaching the distal phalanx to the claw capsule around parturition (Tarlton et al., 2002; Knott et al., 2007), mobilization of adipose tissue from the digital cushion in the rise to peak milk yield (Bicalho et al., 2009; Newsome et al., 2016) and excessive pressures on the corium arising from external environmental factors (Nuss et al., 2019).

The role of subacute inflammation during the transition period has been highlighted as a possible mechanism underlying the risk of poor health outcomes in dairy cows (Bradford et al., 2015). It is believed that all cows experience some degree of systemic inflammation in the days after parturition and that the extent of such inflammatory processes may dictate the risk of subsequent disease (Bradford et al., 2015). Subacute systemic inflammation around the time of parturition may affect physiological processes in the hoof, such as lipolysis of the digital cushion or weakening of the suspensory apparatus, which could thereby predispose a cow to CHL (Newsome et al., 2016). It is therefore possible that the use of nonsteroidal anti-inflammatory drugs (**NSAID**) at parturition could limit the extent of subacute inflammation and reduce the probability of lameness.

Previously, NSAID have been shown to improve cure rates for the treatment of individual cases of CHL (Thomas et al., 2015), indicating these products may have a role in treatment as well as prevention of lameness. Because it has been shown that once cows become lame, they have an increased lifetime risk of lameness (Randall et al., 2016, 2018a), and it has been hypothesized that inflammation may contribute to pathological change in the hoof (Newsome et al., 2016; Wilson et al., 2021), it is therefore possible that ongoing use of NSAID at treatment could also reduce the probability of lameness in later life (Newsome et al., 2016). Consequently, the prevention of heifers first becoming lame and early intervention when lameness occurs, both appear critical in ensuring that these animals are not predisposed to a future lifetime of lameness (Randall et al., 2016, 2018a). If the prevention of lameness or early effective treatment is achieved successfully, then it may be possible to minimize the predisposing effect that lameness has on the animal's future lifetime probability of lameness occurrence.

Our objectives were to investigate the effects of routine, long-term treatment with NSAID at first and subsequent calvings and during treatment for lameness, on the future probability of lameness (primary objective) and culling (secondary objective). We tested this in a randomized controlled trial (**RCT**) over 34 mo; a cohort of dairy heifers, enrolled at first parturition, were randomly allocated to one of 4 intervention groups, to evaluate the effect of NSAID administered on the lifetime probability of lameness and culling.

## MATERIALS AND METHODS

### Study Design

An RCT was designed and conducted in accordance with the REFLECT guidelines (O'Connor et al., 2010), to investigate the efficacy of routine and long-term administration of NSAIDs in the treatment and prevention of lameness. The study was conducted with permission from the University of Nottingham, School of Veterinary Medicine and Science Ethics Committee (Reference No: 1913 161208). The use of the NSAID, ketoprofen in the study was granted approval by the UK Veterinary Medicines Directorate under an Animal Test Certificate Type S (Reference No: ATC-S-090).

To assess our primary objective, the primary outcome measure was lameness state (defined by lameness score) over time (repeated measures of lameness within cow). Our null hypothesis stated that the strategic administration of NSAID at first and subsequent calvings and when treating animals for lameness would have no effect on the lifetime probability of lameness in the study population.

To assess our secondary objective, the secondary outcome measure was time to culling measured at the cow level. Our null hypothesis stated that the strategic administration of NSAID at first and subsequent calvings and when treating animals for lameness would have no effect on the risk of culling in the study population.

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 125 animals would detect an absolute noninferiority

or superiority margin of 12% 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 125 animals per treatment group over the 34-mo period.

### Study Herd and Herd Management

The study population was comprised of a cohort of Holstein heifers within a single commercial dairy herd, that were enrolled at first calving. The herd consisted of 490 milking cows and was located in North Nottinghamshire, England. The farm was selected based on the quality of management and data recording, proximity to the University of Nottingham and willingness of the farm owners to participate in and comply with the protocol for the duration of the study. Once enrolled, animals were monitored throughout the study period of January 8, 2018, to October 23, 2020.

All milking and dry cows were continuously housed with access to stalls containing a rubber mat surface and a bedding blend of sawdust and lime (bedded twice daily to a thickness of approximately 3 cm). Animals were fed a TMR formulated to support a milk yield of 48 L, being primarily comprised of maize and grass silages, rapeseed meal, and wheat. A concentrate was fed individually in the parlor, with animals receiving 3 kg of concentrate in the parlor daily up to 120 DIM, unless they yielded over 50 L of milk, in which case they would receive 4 kg of concentrate daily. After 120 DIM, animals were reduced on a 30-d basis to 0.5 kg of concentrate fed in the parlor daily for the last month of lactation (based on expected drying-off date).

The flooring throughout the animal environment was grooved concrete, which was cleaned by mechanical scraping with a tractor twice daily. Lactating cows were housed in one of 3 barns depending on stage of lactation (early, mid, or late lactation). The early-lactation group housed animals from calving until they were diagnosed as pregnant by a veterinarian. The mid-lactation group housed animals from positive pregnancy diagnosis until 250 DIM if multiparous, or until dry-off if primiparous. The late-lactation group housed multiparous animals from 250 DIM to dry-off or cull; heifers would not be in this yard space unless marked for culling. The yards were stocked at 90, 95, and 105, respectively, in terms of cows per 100 stalls. Animals in the early-lactation yard had access to 2 feed passageways measuring 4.9 m wide by 66 m long, and 2 passageways between the stall bunk areas of 4 m wide by 66 m long. Stalls in the early-lactation yard measured 1.2 m wide with an accessible bed length of 1.8 m. Animals in the mid-lactation or late-lactation yards had access to 2 or one feed passageway, respectively, measuring 4.9 m wide by 45.5 m long, and 2 stall bunk passageways measuring 3.6 m wide by 45.5 m long. Stalls in the mid-lactation and late-lactation yards measured 1.12 m wide with an accessible bed length of 1.7 m. Dry cows were housed within one yard of identical passageway dimensions to those in the late-lactation group at a stocking rate of no greater than 95 cows per 100 stalls. Dry cows had access to one feed passageway and one stall bunk passageway. Dry cows that were within 3 wk of their expected calving date were housed in one of 2 deep straw-bedded yards that were identical in structure. Here, they had access to a feed passageway (4.9 m wide by 20 m long for each yard), which was scraped mechanically once daily. All cows were milked 3 times a day through a rotary parlor, and the mean 305-d milk yield was ~11,600 kg. Access to the rotary parlor was gained through a collecting yard 31 m long by 6 m wide (with a grooved concrete floor) in which the animals would be mustered and managed in their respective groups.

All cows received a routine maintenance hoof trim at each dry-off according to the protocol described by Toussaint Raven (1985) with the modifications described by Archer et al. (2015) and Stoddard (2018), in which toe length is preserved and a wider model is taken respectively. This was completed irrespective of treatment group, with all animals receiving the same procedure. Lactating cows were walked through an automated hoof bath containing 2% formalin at each milking to control digital dermatitis (Jacobs et al., 2019). The footbath was automatically emptied, cleaned, and refilled after every 120 cow passages.

### Enrollment and Retention

All heifers that were due to calve for the first time between January 8, 2018, and June 22, 2020, were eligible for recruitment, irrespective of their lameness state. Animals were allocated to one of 4 treatment groups using a block randomization procedure based on the animal's expected calving date (calculated from insemination and pregnancy diagnosis) as follows. Animals were listed in chronological order of expected calving date from the earliest to the latest for a 4-mo period. Animals were grouped chronologically into fours based on the expected calving date and within each group, randomly allocated one of the 4 treatments, using an online random block generator (Haahr, 2012). Randomization, allocation to group and enrollment was conducted by a single operator (JPW).

Animals remained in the study until culling or the study ended. Causes of animals exiting the trial such

**Table 1.** A description of the adapted AHDB lameness scoring system first described by Thomas et al. (2015) and used in a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and the subsequent risk of culling

| 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 on 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 on affected limb and a distinct decrease in stance duration. Limb flight on 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 on affected limb and very short stance duration. Limb flight on nonaffected limb rapid and walking velocity reduced such that cow cannot keep up with healthy herd. Back raised. |
| 3b | Minimal or nonweight bearing on affected limb. Back raised. Reluctant to walk without encouragement. |

that they were excluded from analysis were as follows: heifers that aborted or calved more than 14 d earlier than their expected first calving date; heifers that had severe calving difficulties or illness at first calving, which resulted in culling; and heifers that displayed dangerous behaviors that risked either injury to themselves or to the investigators during the implementation of the study design. Throughout the study, all animals intermingled and were managed within the main herd and hence, subjected to all routine day-to-day management procedures.

### Lameness Identification

Lameness scoring for the identification of animals requiring treatment was conducted by one of 2 trained technicians who were assessed in annual audits to evaluate level of agreement (as determined by Cohen's Kappa and Gwet's AC1); retraining was conducted if required. To identify lame animals throughout the study (and therefore those eligible for treatment) all lactating animals were lameness scored at 14-d intervals (±48 h). The lameness scoring system described by Thomas et al. (2015) was used, as outlined in Table 1; animals were identified as lame if they were allocated a score of 2 or 3. Animals were allocated a lameness score as they exited the rotary platform on a flat and level concrete surface for any number of strides or time required for the visual assessment of their locomotion.

### Treatment Groups

The RCT was designed to evaluate 4 different approaches to the treatment and prevention of lameness. Heifers were assigned to one of 4 treatment groups (Table 2), before first calving, and they remained in that group for the duration of their time in the herd or until the study ended. The treatment groups and their respective regimens were as follows:

- Group 1 animals received a therapeutic trim (as described below) and a wooden hoof block was applied to the sound claw if deemed necessary by the operator, every time they were identified and treated for lameness.
- Group 2 animals received a therapeutic trim (as described below), a wooden hoof block if deemed necessary by the operator, and a 3-d course of the NSAID ketoprofen (with a single dose administered daily; Dinalgen, 150mg/mL, Bayer PLC, administered by deep intramuscular injection, dose rate of 14 mL/animal per day), each time they were identified and treated for lameness.
- Group 3 animals received a therapeutic trim (as described below), a wooden hoof block if deemed necessary by the operator, and a 3d course of the NSAID ketoprofen (with a single dose administered daily) every time they were identified and treated for lameness (dose as for group 2). In addition, animals in this group, received a 3-d course of the NSAID ketoprofen after each and every calving event (first dose administered 24–36 h after calving, with 2 further doses 24 and 48 h after the first dose; Dinalgen, 150 mg/mL, Bayer PLC, administered by deep intramuscular injection, dose rate of 14 mL/animal per day).
- Group 4 animals received a 3-d course of the NSAID ketoprofen (with a single dose administered daily) every time they were identified with lameness (dose as for group 2). No therapeutic trim or hoof block was administered unless they were scored as severely lame (i.e., score ≥3a).

### Treatment Routines

Animals identified as lame (scores 2 or 3) were treated within 72 h of identification by 1 of 3 trained operators. Three trained operators undertook all lameness treatments for the duration of the study; hoof trimming

**Table 2.** A summary of the 4 treatment regimens applied in a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs (NSAID) in the treatment and prevention of lameness and the subsequent risk of culling

| Treatment group | Treatment trim when identified lame | 3-d course of NSAID when identified lame | 3-d course of NSAID at first and subsequent calvings |
|---|---|---|---|
| 1 | Yes | No | No |
| 2 | Yes | Yes | No |
| 3 | Yes | Yes | Yes |
| 4 | No (unless severely lame) | Yes | No |

protocols and operators were reviewed on an annual basis by a specialist external hoof care auditor (NJB) to ensure consistency and best practice in trimming technique was maintained. Operators who conducted hoof trimming and treatments were partially blinded to treatment group. To limit the potential for bias during trimming of animals in groups 1, 2, and 3, treatment group was only identified when the trim and treatment (e.g., the application of a hoof block) was complete. The practicalities of implementing the complex protocol over a prolonged period of time prevented complete blinding.

Animals were trimmed using an approach based on the Dutch five-step method (Toussaint Raven, 1985) with the adaptations described by Archer et al. (2015; longer toe length) and Stoddard (2018; deeper, wider model). Both the lame limb and the contralateral limb were examined in all animals. A painful claw was identified by CHL presence or the use of hoof testers (which use pressure to aid lameness-causing lesion detection, as described by Pedersen and Wilson, 2021). Lesions were classified as follows:

- SH: incorporation of hemorrhage into horn production, affecting any sole region of the claw
- SU: ulceration of the corium, affecting any sole region of the claw
- WLD: hemorrhaging, separation or ulceration, affecting the white line region of the claw
- Digital dermatitis: presentation in any form causing lameness
- Other lameness-causing lesion

All lesions were recorded, and the operator administering treatment would allocate the primary lameness-causing lesion according to severity. Where their application was considered necessary as part of the treatment protocol, wooden hoof blocks were applied using a 2-part adhesive (Mini Moo Gloo, Integra Adhesives Inc.) following the cleaning and drying of the healthy contralateral claw. Blocks were applied such that the diseased region of the effected claw was lifted from the ground by a minimum of 2 cm. Blocks were not applied to diseased claws. If an animal was in treatment groups 2, 3 or 4, the first lameness treatment dose of NSAID was administered in the hoof trimming crush at the end of the assessment and treatment protocol. Two hook-and-loop fastener leg bands were applied to the left hind legs of animals denoting a requirement for further NSAID administration. Different colored leg bands were used to indicate the days of future treatment (e.g., blue indicated a future NSAID treatment was required on Tuesday). Once animals had been milked in the afternoon of the 2 following days, subsequent doses of NSAID were administered and a leg band removed to denote the animal had been treated that day. The animal's identification was cross checked against a list of individuals requiring treatment for each day, to ensure all animals received their allocated dose of NSAID at the correct time. Animals suffering from infectious causes of lameness (e.g., digital dermatitis) received the same treatment protocol as described previously, but with the addition of the topical antimicrobial Thiamphenicol (TAF spray, 28.5 mg/g, Dechra Pharmaceuticals PLC, applied to sufficiently cover the skin of the affected area), once the affected region had been cleaned and dried.

Any animal suffering from a severe lesion causing lameness were referred for veterinary intervention following initial first aid treatment. Animals requiring veterinary intervention received treatment under local anesthetic, treatment was composed of a preliminary trim and application of a wooden hoof block if required. These animals were treated for lameness in line with the recommendations of the attending veterinarian (who was unaware of treatment group), meaning that NSAID could be prescribed if deemed appropriate by the clinician (i.e., for welfare or anti-inflammatory reasons). Data were collected from these animals in line with the study protocol.

Following lameness treatment, animals entered a treatment refractory period of 28 d to allow time for recovery, beginning on the day of lameness diagnosis. Animals could only be retreated within this refractory

period if they were deemed to be severely lame (score ≥3a) by farm staff or study technicians. This additional treatment would entail a therapeutic trim and application of a hoof block to the sound claw.

Farm staff responsible for the day-to-day care of animals were blind to treatment group (and the study protocol as a whole) but were responsible for assisting with the administration of NSAID at calving and when animals were treated for lameness. Masking was maintained as far as was practical by identifying animals requiring NSAID treatment with leg bands and providing pre-prepared syringes of NSAID (i.e., no further information was provided about the study protocol).

Lame animals identified by farm staff outside of the routine lameness scoring, that were not in the refractory period, had treatments determined by the protocol for the group to which they belonged. That is, animals received the same treatment protocol throughout the study, regardless of how or when they were identified for treatment (unless they were within a refractory period following treatment). This treatment would be administered by one of the 3 trained operators. All hoof blocks were removed 24 d (±48 h) after application if they were still present. Any blocks that fell off before this point were not reapplied unless required for an interim lameness treatment as described above.

### Lameness Outcome Scores

To ensure no bias arose from knowledge of treatments, all study animals were scored for lameness as an outcome measure on a 14 d (±48 h) interval throughout the study, by one of 2 trained, independent lameness scorers (i.e., during each 2-wk period, the herd was scored twice by different observers, once to identify animals for treatment and once as an outcome measure for the study). These outcome lameness scores were conducted at milking, as animals exited the rotary platform using the same methodology as the lameness detection scores previously described. These scores were used in the statistical analyses to evaluate differences between treatment group. The operators conducting the outcome assessment were not associated with any other aspects of the study, were blinded to treatment group protocols and allocation, and conducted the herd lameness score independent to any other aspects of study administration. Cows with hoof blocks were lameness scored during the time the block was in place and it was noted that the block was present; however, this score was not used in the final data set. The 2 outcome lameness scorers were subjected to annual audits as previously described for the other scoring technicians. All 4 lameness scorers (both outcome scorers and those identifying animals for treatment) underwent the same initial training regimen together, to ensure uniformity in the base line of detectible lameness levels.

### Data Collection and Descriptive Analysis

Data were collated on a 14 d (±48 h) basis and stored in a relational database (Microsoft Access, Microsoft Corp., 2016). The major outcomes of interest were occurrences of lameness (measured through blinded routine lameness scoring as previously described) and time to culling (determined by on farm recordings of culling or death). Lameness was defined as a binary variable for each 14 d score; cows were categorized as lame if their score was ≥2a and nonlame if their score as <2a. Severe lameness was defined in a similar manner but using a threshold for lameness of ≥3a. Time to cull was identified as the days elapsed between the animal's first calving date and the day of slaughter (irrespective of whether the animal was dispatched on farm or processed at an abattoir) as recorded in the herd management database by farm staff. The reason for culling was determined from farm recordings, wherein the primary reason for slaughtering the animal (either on farm dispatch, or slaughter at an abattoir) was described. Weeks on study was defined as the number of weeks that elapsed between an animal first calving (entering the study), and the date of slaughter or trial ending (exiting the study).

To ensure that there was no influence on the subjectivity of either the treatment or the outcome scores, the outcome lameness scores were stored and managed separately from the remaining data. Data handling and analysis were carried out using Microsoft Excel 2016 (Microsoft Corp., 2016) and RStudio V1.2.5033 (https://r-project.org). Data collated included calving dates, treatment groups, lameness scores, time on the study and culling date. Initial data handling, and screening was undertaken to identify missing or anomalous data. Anomalous lameness scores were reviewed to determine the origin of any error before inclusion or exclusion from the final data set, as was the recorded cull data.

### Statistical Modeling

To evaluate the study hypotheses, 3 statistical models were constructed. Two mixed-effects logistic regression models were used to evaluate the effect of treatment group on the ongoing probability of lameness (as identified by a lameness outcome score ≥2a) or severe lameness (as identified by a lameness outcome score ≥3a). A Cox proportional hazards survival model used

to investigate the effect of treatment group on time to culling. The mixed-effects logistic regression models took the following form:

$$\text{Lameness}_{ij}\ (1 = \text{lame}, 0 = \text{nonlame}) \sim \text{Bernoulli}\ (\mu_{ij})$$

$$\text{logit}\ (\mu_{ij}) = \beta_0 + \beta_1 x_{ij} + \beta_2 x_j + u_j$$

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

where $\mu_{ij}$ was the probability of an animal being lame or severely lame at the $i$th score of the $j$th cow, $\beta_0$ the model intercept, $x_{ij}$ a matrix of covariates linked to each lameness score (DIM or week on study, both of which were tested as $\log^{10}$ polynomial terms in the models to power 4), $\beta_1$ the coefficients for $x_{ij}$, $x_j$ a matrix of covariates linked to each cow (e.g., treatment group), $\beta_2$ the coefficients for $x_j$, $u_j$ represented a random effect for the $j$th cow and $\sigma^2$ the variance of the random effects $u_j$.

Covariates were deemed significant and remained in the model when $P < 0.05$. Interactions between significant covariates were tested and retained in the model when $P < 0.05$. Investigation of model fit was made by assessing realized discrepancies between cumulated predicted probabilities and observed outcomes (Gelman et al., 1996) and the assessment of normality of random effects. Because random effects were over dispersed, the final models were repeated with outlying cows omitted (>10 occurrences of lameness during the study period) to check for meaningful changes in model parameters or their interpretation. Predictions from the final models were visualized graphically to illustrate the probability of lameness or severe lameness by treatment group for the duration of the study. A term for cow was included as a random effect to account for repeated measurements of lameness outcome within cow over time.

A conventional Cox proportional hazards was constructed using the survival and survminer packages in R, the model took the following form:

$$h(t) = h_0(t) \times \exp(\beta_1 \text{x}_1 \ldots \beta_p x_p),$$

where $t$ represented the survival time to culling, $h(t)$ the hazard function which was dependent on a baseline hazard $h_0(t)$ and $p$ covariates ($\text{x}_1 \ldots x_p$) with $\beta_1 \ldots \beta_p$ the related coefficients.

Covariates were deemed significant and retained in the model when $P < 0.05$. Evaluation of the proportional hazard's assumption and model fit was undertaken by visual assessment of Schoenfeld residuals, the log-log curves and delta betas (Schoenfeld, 1982; Grambsch and Therneau, 1994). The data were visualized graphically using Kaplan-Meier plots to illustrate time to culling by treatment group.

## RESULTS

### Study Denominators

Precalving randomization led to the following recruitment: 132 animals to group 1, 132 to group 2, 132 to group 3 and 132 to group 4. Of those, 116 in group 1, 120 in group 2, 112 in group 3, and 118 in group 4 successfully calved within 2 wk of their expected calving date and continued in the study. Subsequently 20 cows (5 from group 1, 3 from group 2, 6 from group 3, and 6 from group 4) were removed because of severe issues at first calving which resulted in them not being presented for lameness scoring and 8 animals (0 from group 1, 0 from group 2, 6 from group 3, and 2 from group 4) were removed because they posed a danger to farm staff or technicians during handling for lameness treatment. These reasons for exit were considered to have occurred at random (i.e., they were not linked to treatment group). Therefore, a total of 438 animals were included in the final analysis with 111 in group 1, 117 animals in group 2 animals, 100 animals in group 3, and 110 animals in group 4. No adverse events associated with administration of the treatment protocol were recorded in any of the treatment groups.

### Descriptive Statistics

Study animals received 973 lameness treatments (271 under group 1 regimens, 254 under group 2, 151 under group 3, and 297 under group 4). From the lameness treatment records, 99 cases of lameness were associated with infectious causes (e.g., digital dermatitis), 675 with CHL (SH, SU, WLD) and 27 from other causes (e.g., musculoskeletal injury). In 172 cases no visible claw lesion was present, and the cause of the lameness was unknown. Outcome lameness scores were collated for the entire study period (146 wk), yielding 13,886 individual lameness scores. A summary of the treatments administered, and outcome lameness scores are provided in Table 3.

During the study period, a total of 106 study animals were culled (38 from group 1, 24 from group 2, 17 from group 3, and 27 from group 4). Primary reasons for culling as recorded by farm staff included fertility (n = 50), lameness (n = 8), udder health (n = 8), other (n = 22), and no recorded reason (n = 18). A description of the culling reasons by treatment group is described in Table 4. A description of the occurrence of culling across lactations is given in Table 5.

**Table 3.** Descriptive statistics of the lameness data derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and the subsequent probability of culling[1]

| Variable | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Proportion of outcome lameness scores recorded as lame | 892/3,605 | 870/4,044 | 564/2,899 | 859/3,338 |
| Proportion of outcome lameness scores recorded as severely lame | 79/3,605 | 55/4,044 | 23/2,899 | 70/3,338 |
| Number of lameness treatments administered | 271 | 254 | 151 | 297 |
| Number of animals that did not receive a lameness treatment | 28 | 31 | 42 | 26 |
| Mean lameness treatments administered per animal | 2.13 | 1.90 | 1.63 | 2.48 |
| Minimum–maximum | 0–19 | 0–9 | 0–13 | 0–17 |
| Number of hoof blocks applied | 87 | 82 | 68 | 34 |
| Number of additional "first aid" lameness treatments required | 4 | 7 | 2 | 19 |
| Number of veterinary referrals for lameness | 2 | 1 | 0 | 1 |
| Number of animals contributing lameness scores in their second lactation | 65 | 73 | 68 | 55 |
| Number of animals contributing lameness scores in their third lactation | 3 | 6 | 5 | 4 |
| Number of animals requiring more than one lameness treatment | 53 | 46 | 34 | 60 |

[1]The data set this is constructed from contains 13,886 individual lameness scores from 438 animals over a 34-mo period. Animals were recruited at first calving, and lameness and calving treatments were administered according to the treatment group to which the animal belonged.

### Statistical Modeling

Model A is a mixed-effects logistic regression model to evaluate the probability of lameness (score $\geq$ 2a). Final results of model A are provided in Table 6. Compared with cows in group 1, cows in group 3 were less likely to become lame during the study period [odds ratio (**OR**) 0.66, $P = 0.03$]. The probability of lameness over time for cows in each treatment group is illustrated in Figure 1. Model fit was assessed to be good, and omission of outlying cows had no effect on model parameters (<5% alteration in coefficients and no changes in significance).

Model B is a mixed-effects logistic regression model to evaluate the probability of severe lameness (score $\geq$3a). Final results of model B are provided in Table 7. Compared with cows in group 1, cows in group 3 were less likely to become severely lame during the study period (OR = 0.28, $P = 0.04$). The probability of severe lameness over time for cows in each treatment group is illustrated in Figure 2. As for model A, model fit was good.

Model C is a Cox proportional hazards model for survival to culling. Final results of model C are provided in Table 8. Compared with cows in group 1, cows in groups 2 and 3 were at a reduced risk of culling during the study period (hazard ratio = 0.55, $P = 0.02$ and 0.56, $P < 0.05$, respectively). A Kaplan-Meier plot to illustrate survival time to culling by treatment group is presented in Figure 3. Investigations of model fit indicated that the model assumption of proportionality of hazards was met, and residual analysis indicated fit was good.

## DISCUSSION

To the authors knowledge, this RCT is the first to investigate the effect of a continuous clinical intervention on the probability of lameness over a period longer than one year (Groenevelt et al., 2014; Thomas et al., 2015;

**Table 4.** Descriptive statistics of the culling data derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and the subsequent risk of culling[1]

| | | Reason for culling | | | | |
|---|---|---|---|---|---|---|
| Group | Parity | Udder health | Fertility | Lameness | Other | No recorded reason |
| 1 | 1 | 3 | 10 | 2 | 3 | 2 |
| | 2 | 1 | 9 | 0 | 2 | 5 |
| | 3 | 0 | 0 | 1 | 0 | 0 |
| 2 | 1 | 0 | 10 | 2 | 4 | 5 |
| | 2 | 1 | 0 | 0 | 2 | 0 |
| 3 | 1 | 1 | 3 | 2 | 4 | 3 |
| | 2 | 0 | 2 | 0 | 1 | 1 |
| 4 | 1 | 1 | 12 | 1 | 4 | 2 |
| | 2 | 1 | 4 | 0 | 2 | 0 |

[1]The data set this is constructed from contains 106 cull recordings from 438 animals over a 34-mo period. Animals were recruited at first calving, and lameness or calving treatments were administered according to the treatment group to which the animal belonged. Culling reasons were determined by farm managers with no input from study administrators.

**Table 5.** Descriptive statistics of the culling data pertinent to survival time derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and the subsequent risk of culling[1]

| Group | Parity | Mean DIM at slaughter | Number of animals slaughtered |
|---|---|---|---|
| 1 | 1 | 354 | 20 |
| | 2 | 328 | 17 |
| | 3 | 78 | 1 |
| 2 | 1 | 405 | 21 |
| | 2 | 237 | 3 |
| | 3 | NA[2] | 0 |
| 3 | 1 | 372 | 13 |
| | 2 | 375 | 4 |
| | 3 | NA | 0 |
| 4 | 1 | 358 | 20 |
| | 2 | 325 | 7 |
| | 3 | NA | 0 |

[1]The data set this is constructed from contains 106 cull recordings from 438 animals over a 34-mo period. Animals were recruited at first calving, and lameness or calving treatments were administered according to the treatment group to which the animal belonged. Culling reasons were determined by farm managers with no input from study administrators.

[2]NA = not applicable.

**Table 6.** The output from a mixed-effects logistic regression model investigating the effect of treatment group on the ongoing probability of lameness (lameness score ≥2a) derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness[1]

| Characteristic | Estimate | Odds ratio | SE | *P*-value |
|---|---|---|---|---|
| Intercept | −7.01 | <0.01 | 1.54 | 5.44E-06 |
| Treatment group 1 | Reference | — | — | — |
| Treatment group 2 | −0.29 | 0.75 | 0.17 | 0.10 |
| Treatment group 3 | −0.42 | 0.66 | 0.19 | 0.03 |
| Treatment group 4 | 0.03 | 1.04 | 0.18 | 0.83 |

[1]The data set this model is constructed from contains 13,886 individual lameness scores from 438 animals over a 34-mo period. Week on study (logged to base 10) and polynomial terms for logged week on study (to power 3) were also included in this final to control for the nonlinear baseline risk of lameness over time. Animals were recruited at first calving, and treatment group represents 4 different treatment protocols administered at lameness and calving.

Mahendran et al., 2017; Warner et al., 2021) and is in fact one of the longest disease treatment RCT in cattle which we can identify in the literature. Similar to many of the endemic production diseases of cattle, lameness is known to have cumulative and lifelong repercussions (Newsome et al., 2016; Randall et al., 2016, 2018a; Wilson et al., 2021), hence long-term studies are vital if we are to further elucidate treatment and prevention strategies, which lead to long-term benefits on farm. Our results indicated a significant benefit when NSAID are routinely administered at first and subsequent calvings and every time animals are treated for lameness. Compared with animals treated by conventional best practice methods (group 1; Figure 1), we would expect that a cohort of animals receiving the group 3 treatment protocol would see an absolute reduction in population lameness prevalence of approximately 10%, if both groups started the program with a similar lameness prevalence. That is, our results suggest that the administration of NSAID at first and subsequent calvings alongside lameness events (in conjunction to therapeutic trimming and appropriate application of hoof blocks) would result in one in 10 fewer cows being identified lame when assessed for lameness prevalence by lameness scoring. Furthermore, the same intervention reduced the risk of these animals being culled. If the results of this study are generalizable to the wider population, this strategic use of NSAID has the potential to substantially reduce the overall prevalence of lameness in a dairy herd by an absolute value of 10% (i.e., 10 in 100 fewer cows would be lame on any

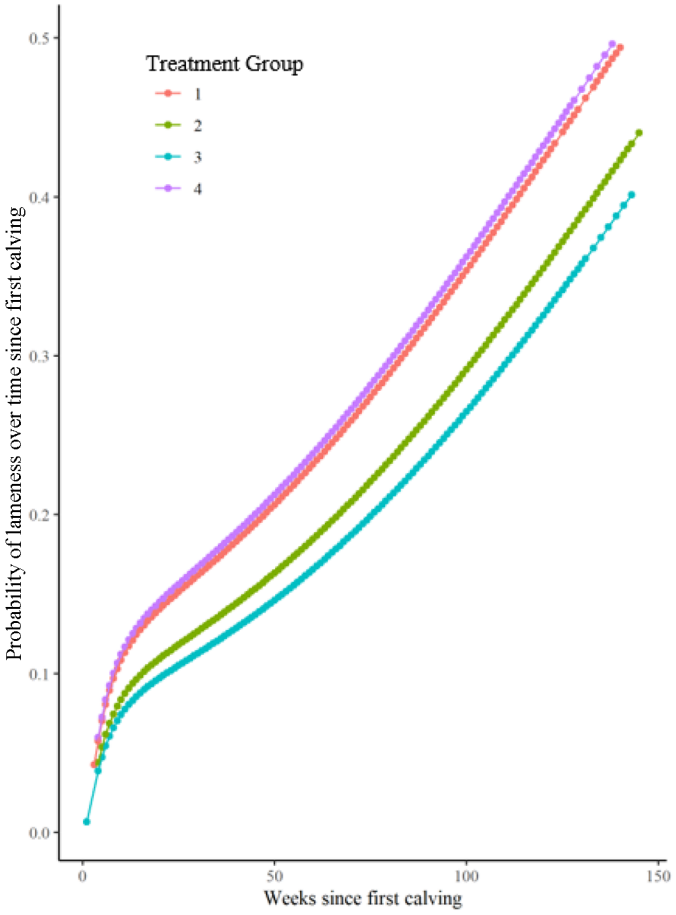


**Figure 1.** Graphical illustration of predictions from the mixed-effects logistic regression model investigating the effect of treatment group on the probability of lameness (lameness score ≥2a), derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness. The data set contained 13,886 individual lameness scores from 438 animals over a 34-mo period

**Table 7.** The output from a mixed-effects logistic regression model investigating the effect of treatment group on the ongoing probability of severe lameness (lameness score ≥3a), derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness[1]

| Characteristic | Estimate | Odds ratio | SE | *P*-value |
|---|---|---|---|---|
| Intercept | −23.70 | 5.08E-11 | 6.69 | 3.93E-04 |
| Treatment group 1 | Reference | — | — | — |
| Treatment group 2 | −0.50 | 0.61 | 0.51 | 0.32 |
| Treatment group 3 | −1.27 | 0.28 | 0.60 | 0.04 |
| Treatment group 4 | −0.30 | 0.74 | 0.53 | 0.57 |

[1]The data set this model is constructed from contains 13,886 individual lameness scores from 438 animals over a 34-mo period. Week on study (logged to base 10) and polynomial terms for logged week on study (to power 3) were also included in this final to control for the nonlinear baseline risk of lameness over time. Animals were recruited at first calving, and treatment group represents 4 different treatment protocols administered at lameness and calving.

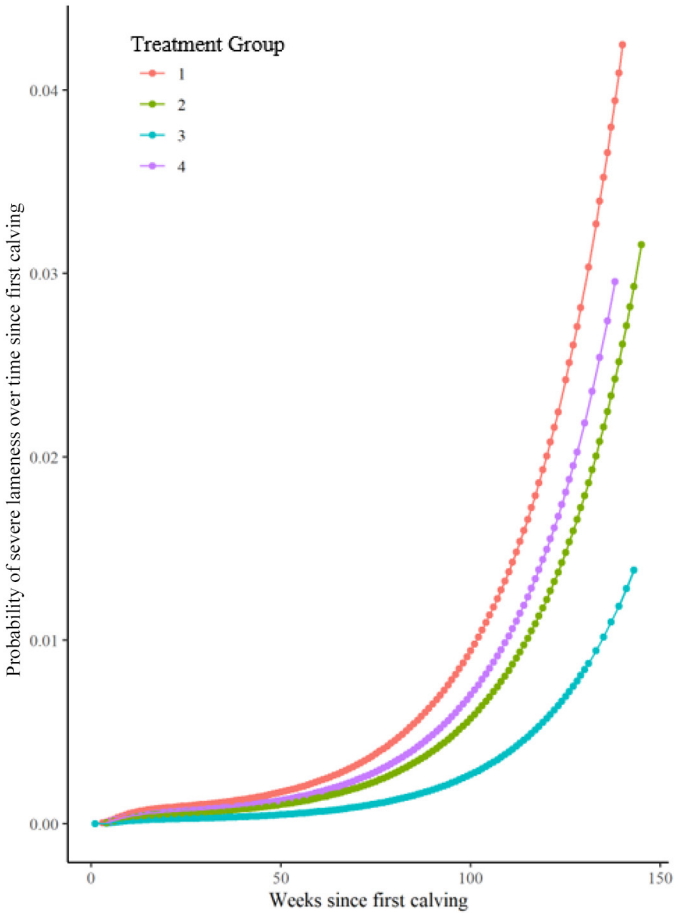


**Figure 2.** Graphical illustration of predictions from the mixed-effects logistic regression model investigating the effect of treatment group on the probability of lameness (lameness score ≥3a), derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness. The data set contained 13,886 individual lameness scores from 438 animals over a 34-mo period.

day of assessment), and the prevalence of severe lameness by 3% (i.e., 3 in 100 fewer cows would be severely lame on any day of assessment; Figure 2). Given the considerable welfare implications of lameness (Whay and Shearer, 2017) and the high prevalence of lameness in most dairy nations (Von Keyserlingk et al., 2012; Ranjbar et al., 2016; Randall et al., 2019), we consider the potential benefits of this intervention for the dairy industry are considerable.

Importantly, the design of this study, a randomized controlled trial conducted in accordance with best practice standards (REFLECT guidelines), means that results were unlikely to be affected by bias or confounding; RCT are considered to provide strong evidence of a causal effect (Evans, 2003; Backmann, 2017). No negative effects on health and welfare parameters were noted anecdotally with the intervention implemented as part of the group 3 protocol.

The primary outcome measure in this study was lameness score assessed on a 14 d (±48 h) interval, no other metrics of NSAID intervention on distal limb anatomy were recorded, meaning that the mechanism behind the causal effect of the NSAID intervention we tested cannot be elucidated from this study. We hypothesize several mechanisms through which the observed benefits could occur. The extent of systemic inflammation during transition is considered to be associated with the risk of an individual experiencing disease during lactation (Bradford et al., 2015). The reduction of systemic and local inflammation in the hoof capsule associated with NSAID administration postpartum (as would be expected in line with our group 3 intervention) could be a key driving factor behind the reduction in lameness observed. It is possible that systemic inflammation around calving has a detrimental effect on the functional anatomy of the hoof, in early lactation, leading to increased susceptibility to lameness. With increased susceptibility, additional management factors (e.g., housing conditions and increased standing times) may exacerbate the pressures exerted through the hoof leading to an increased risk of CHL (Knott et al., 2007).

We hypothesize that this inflammation can lead to a predisposition to lameness in the animals' immediate and distant future, through immediate changes to anatomic structures and long-term deterioration to the functionality of the anatomy respectively. The reduction in lameness probability observed in those animals receiving NSAID at calving (group 3 protocol) could be caused in the short term by a protective mechanism through which the range of fatty acids contained within the digital cushion (Newsome et al., 2021) are not utilized as inflammatory mediators as they commonly can be in other biological models (Calder, 2006; Bradford et al., 2015; Contreras et al., 2017). Furthermore, the

**Table 8.** Results of a Cox proportional hazards model for time to culling, derived from a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and risk of culling[1]

| Model term | Coefficient | Hazard ratio | *P*-value |
|---|---|---|---|
| Treatment group 1 | Baseline | — | — |
| Treatment group 2 | −0.61 | 0.55 (95% CI: 0.33–0.91) | 0.02 |
| Treatment group 3 | −0.58 | 0.56 (95% CI: 0.32–0.99) | <0.05 |
| Treatment group 4 | −0.29 | 0.75 (95% CI: 0.46–1.2) | 0.25 |

[1]The data set on which this model is based consists of 438 animals within a single commercial herd, of which 106 were culled during the study period. Animals were recruited at first calving, and treatment group represents 4 different treatment protocols administered at lameness and calving.

benefits of NSAID administration as per the group 3 protocol may also prevent lameness by negating the effects that adipose tissue metabolism may have on the digital cushion structure (Wilson et al., 2021). The metabolism of digital cushion fatty acids presents 2 risks; first, this release of fatty acids could, in turn, drive the further long-term deterioration of the digital cushion structure through acting as mediators to the inflammatory processes locally (Calder, 2006). Second, the immediate functional anatomy of the digital cushion may be impeded through the thinning of the digital cushion on a short-term basis (Newsome et al., 2016), limiting its capacity to dissipate force during limb loading. Treatment with NSAID in the period immediately after calving (as per the group 3 treatment protocol) may offer protection from thinning and remodeling of the digital cushion by reducing the requirement for inflammatory mediators due to the inhibition of systemic inflammation associated with the transition period. This protection from alterations to digital cushion structure may be the reason why a reduction in lameness probability was observed in animals exposed to the group 3 treatment protocol in comparison to those exposed to the group 1 protocol (OR = 0.66, $P = 0.03$). Further work is needed to confirm or refute these hypotheses and elucidate the origins of the protective effect identified in this study.

The same changes to distal limb anatomy as described above have been suggested to occur at the time of lameness also (Newsome et al., 2016; Wilson et al., 2021). The inflammation associated with CHL has been postulated to stimulate exostosis development (Newsome et al., 2016) and also lead to digital cushion adipose metabolism (Wilson et al., 2021). Within the current study, we implemented the early detection and prompt effective treatment principle (Pedersen and Wilson, 2021). This has already been shown to improve 35-d cure rates (Thomas et al., 2015, 2016) and improve lameness prevalence generally (Groenevelt et al., 2014); however, its relevance to the prevention and management of pathological change to hoof structures is not understood. A previous study conducted by Laven et al. (2008) found no additional benefit on lameness-based outcomes with NSAID administration as part of a lameness treatment protocol. However, in the current study we identified a substantial benefit when used in combination with NSAID administration at calving, this difference may be due to the study population enrolled by Laven et al. (2008) being comprised of animals identified as lame by farm staff. It has previously been shown that producers are less likely to be able to identify early signs of lameness (Leach et al., 2010), meaning that the animals enrolled in the previous study were likely at a later stage in the disease process and may have a degree of pathological change to anatomy already present. We postulate that through early intervention in lameness cases within the current study, that we have reduced any changes to the distal phalanx or the digital cushion through the use of NSAID not only at calving, but also at the earliest point of CHL onset. Further research is required to investigate the effects of lameness treatment regimens on pathological change to distal limb anatomy to either confirm or refute this hypothesis.

The primary outcome measure assessed was lameness score, a subjective human assessment of the pain experienced by the animal during locomotion. Finally, we hypothesize that the observed differences between the group 1 and group 3 protocols may be due to a modulation of the animal's pain signaling pathways. Dairy cattle suffering from CHL have been shown to exist in a state of hyperalgesia (Whay et al., 1998), and it has been demonstrated that NSAID are important in the management of this state of pain (Whay et al., 2005). Animals experiencing a repeated noxious stimulus can undergo pathophysiological changes to the nervous system which causes a transition from acute to chronic pain (Devor, 2006; Greene, 2010; Voscopoulos and Lema, 2010). The transition from acute to chronic pain, does not necessarily require nerve damage to take place, and repeated exposure to inflammation can create the same effect (Devor, 2006; Voscopoulos and Lema, 2010). This transition causes the region affected to become more sensitive to noxious stimuli, meaning

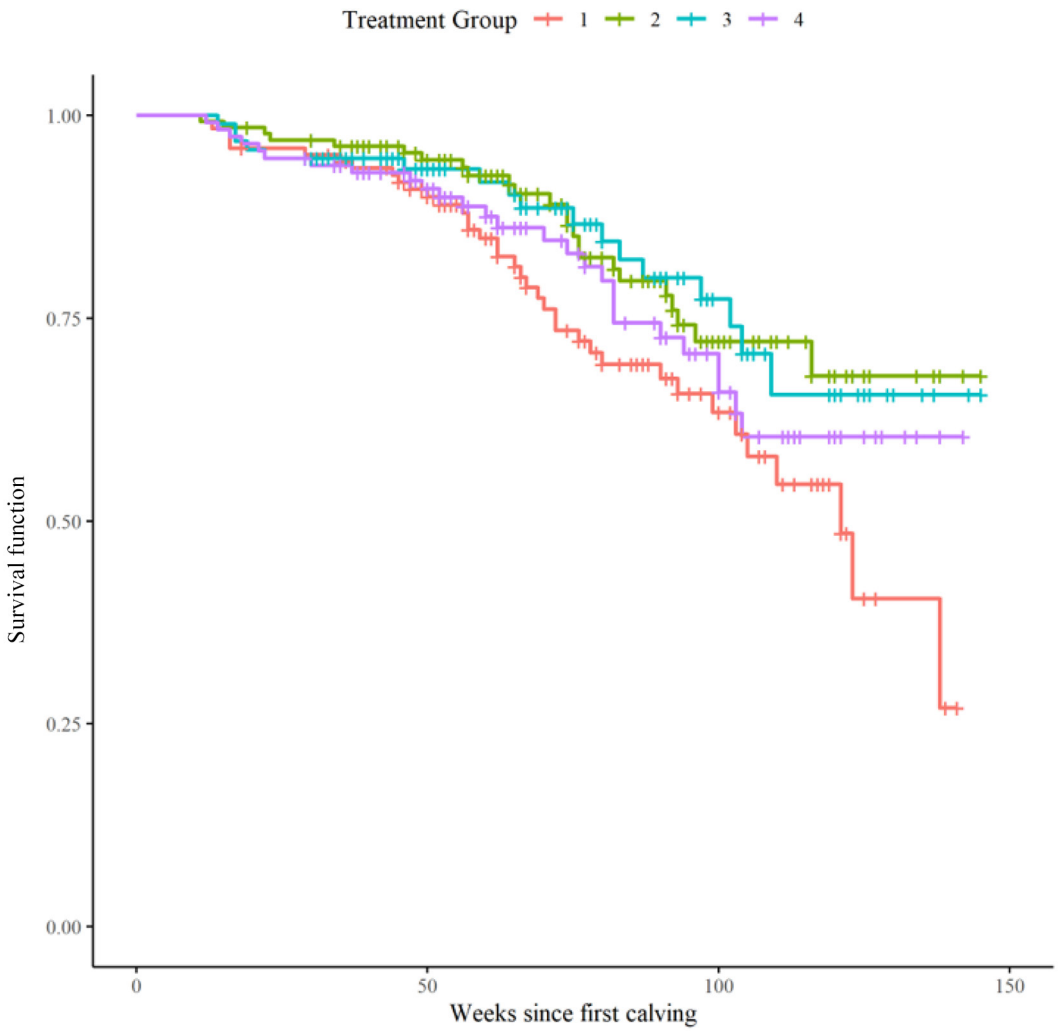


**Figure 3.** Kaplan-Meier plot for the survival analysis of heifers subjected to 1 of 4 lameness treatment regimens over a 34-mo randomized controlled trial investigating the efficacy of nonsteroidal anti-inflammatory drugs in the treatment and prevention of lameness and risk of culling.

that a heightened pain response will be experienced (Bartfai, 2001). This may result in animals experiencing a lower nociceptive threshold, even when free of disease. In addition, NSAID have been shown to prevent the transition from acute to chronic pain (Bartfai, 2001; Samad et al., 2001; Telleria-Diaz et al., 2010). We hypothesize that the benefit observed in group 3 may be derived from the inhibition of this transition from acute to chronic pain associated with inflammation alongside the modulating the pathogenic pathways associated with CHL.

This study was conducted according to best practice standards (REFLECT guidelines) and undertaken on a single, well managed, high yielding commercial dairy unit, which we believe to be representative of good quality housed dairy systems in the United Kingdom. Additional work is required to test whether the interventions we assessed can be generalized to other herds, systems, and locations. Nonlactating dairy cows were not included in the routine scoring and treatment protocol described within this study. Understanding the risks and effects of dry period lameness, may play a role in further improving the effects observed and should be the subject of future investigations. Finally, animals were subject to routine farm management for all other diseases. Some cows may have received short courses of NSAID when treated for diseases other than lameness. Although we have no reason to suspect that these treatments were not randomly distributed between our treatment groups, the extent, if any, to which these treatments influenced our results in unknown.

In conclusion, our results indicate that treatment with NSAID at first and subsequent calvings and every time animals are identified lame, reduced the lifetime prob-

ability of lameness, severe lameness and culling during a 3-yr RCT. We hypothesize that systemic inflammation at the time of calving and localized inflammation at lameness predisposes cows to future lameness and that this is limited by routine treatment with NSAID. Furthermore, a reduction in lameness was associated with the repeated administration of NSAID at painful events (calving and lameness), potentially due to the modulation of pain signaling pathways, which would lead to a substantial improvement to animal welfare. The administration of NSAID at calving and when treated for lameness appears to set animals on a trajectory to experience less lameness, and consequently less pain, in future life. Our results suggest that this approach should be carefully considered by the attending clinician, and if deemed appropriate, recommended for use as a clinical intervention on farm.

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