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ORIGINAL RESEARCH

Evaluation of the use of ketoprofen for the treatment of digital dermatitis in dairy cattle: A randomised, positive controlled, clinical trial

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Abstract

Background: The objective of this study was to evaluate the benefits of administering ketoprofen to cows suffering from active digital dermatitis (DD).

Methods: 158 cows presented with active DD (M1, M2 or M4.1 stage) were randomly allocated to either the control or the treatment group. All cows were treated with topical application of oxytetracycline spray. The treatment group also received an intramuscular injection of ketoprofen (3 mg/kg, Ketofen 10%, Ceva Animal Health). Cows were mobility scored just before they were treated and then again one week later. Information regarding their daily milk production was also collected.

Results: Animals in the control group were at 2.57 (95% confidence interval (CI): 0.82–8.01, $p = 0.10$) times higher odds to be lame at the second evaluation compared to those that received ketoprofen as well. This was a numeric but not statistically significant difference. When only cows that were lame prior to treatment were considered, cows that did not receive ketoprofen were at 20.20 (95% CI: 1.40–291.29, $p = 0.03$) higher odds of remaining lame week post-treatment comparing to cows that did receive ketoprofen. Freshly calved and lame at enrolment cows in the treatment group produced 58.38 ± 1.85 kg per day the week after treatment comparing to freshly calved and lame at enrolment controls that produced 47.89 ± 1.81 kg per day ($p < 0.05$).

Conclusion: The addition of ketoprofen in the treatment of active DD lesions may be beneficial for animal welfare and for animal productivity.

INTRODUCTION

Lameness is one of the most significant problems facing the dairy industry worldwide, having a major impact on cattle welfare, health and production, and leading to substantial economic losses.[1] Lameness has been associated with reduced milk yield,[2] mastitis, and infertility.[3] Lameness has been reported to be prevalent in dairy herds in Europe and North America.[4–6] Within the UK, the mean herd lameness prevalence was recently found to be 31.8%.[7]

Digital dermatitis (DD) is one of the most frequently recorded diseases associated with lameness in dairy cattle. Digital dermatitis is an infectious dermatitis of the digital skin that may be painful to touch. Lesion appearance varies; the typical DD lesions have been described as circumscribed, erosive to papillomatous lesions surrounded by a ridge of hyperkeratotic skin bearing hypertrophied hairs.[8,9] Digital dermatitis lesions can be classified according to the M-stage scoring system which is based on the gross appearance of the lesion[10] and broadly divides lesions into active

lesions (M1, M2 and M4.1) and healing or chronic lesions (M3 and M4, respectively). The multifactorial aetiology of digital dermatitis includes many bacterial pathogens; the most commonly isolated being spirochetes of the *Treponema* spp.[11]

Several regimes have been developed for the treatment of DD. A commonly chosen treatment method in the UK includes the application of an antibiotic spray topically.[12] Non-antibiotic treatments, such as copper sulphate and iodine, have been proven insufficiently effective at achieving a cure, though they may accelerate the recovery rate.[13] Many cases treated with topical antibiotics require repeated treatments.[10]

Some stages of DD are painful, but there has been little research to determine the value of including analgesia in the treatment of DD. The use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of non-infectious claw horn disruption lesions has been investigated[14,15]; however, to the best of our knowledge, there is no evidence regarding their effectiveness in the treatment of DD.

In spite of the steadily increasing introduction of routine preventative measures on farms, the prevalence of digital dermatitis remains high. Given that DD is a painful condition, the use of NSAIDs alongside antibiotic treatment may be justified on welfare and possibly on economic grounds; however, this is yet to be proven. The objective of this randomised, positively controlled study was to explore the potential benefits of a single administration of ketoprofen when treating active digital dermatitis lesions. The study's null hypothesis was that use of ketoprofen alongside treatment with the topical antibiotic spray will not affect animals' mobility and daily milk yield post-treatment.

MATERIALS AND METHODS

Farm selection

A randomised positively controlled trial was approved by the University of Liverpool research ethics committee (VREC828). This study was conducted alongside a larger scale project involving four farms in the North West of England and North Wales. The selection of the farms was based on herd size, the proximity to the University's Leahurst campus, and farmers' willingness to participate in the study. Farm 1 housed milking Holstein cows that were kept in one group regardless of production or lactation stage. On farm 2, the milking cows were split into two groups based on the stage of lactation and milk yield. The low production group was grazed during the summer, as were the dry cows and youngstock. Farms 3 and 4 split their herd into eight and four groups respectively based on parity and lactation stages. Footbaths were used on all farms. Farms 1 and 4 used footbaths of either copper sulphate or formalin; the frequency on Farm 1 was three times a week and on Farm 4 it was conducted daily. Farms 2 and 3 used formalin footbaths only; the frequency on Farm 2 was three times a week and twice daily on Farm 3.

Cow enrolment

Enrolment for this trial occurred from September 2019 to March 2020. Prior to the commencement of this trial, animals had been assessed for approximately 2 months pre-calving and were scheduled to be re-assessed again approximately 1 week, 50–100 days and 170–200 days post-calving (termed: fresh, early lactation and late lactation, respectively). Enrolled cows on either one of the three lactation time points were separated from their group during milking and were mobility scored using the UK Agricultural and Horticultural Development Board (AHDB) 0–3 scale scoring method,[16] predominantly by a single trained assessor (C. Bedford). Cows were given a score of 0 when they walked with even weight-bearing and rhythm on all four feet, and with a flat back; long, fluid strides were possible. Cows that stepped unevenly (rhythm or weight-bearing) or had shortened strides were given a score of 1; affected limb or limbs were not immediately identifiable in that case. Score 2 cows had an uneven weight-bearing on a limb or limbs that was immediately identifiable and/or obviously shortened strides (usually with an arch to the centre of the back). Score 3 cows were unable to walk as fast as a brisk human pace and had signs of a score of 2. All cows were examined for foot lesions in a foot trimming crush. If a DD lesion was found during the examination, it was macroscopically classified using the modified standardised M scoring system with six levels.[10] The examination and the lesion scoring were performed by the same person (A. Anagnostopoulos) for all the animals, who also applied any treatment if needed as is explained below. Cows presented with what is considered to be an active DD lesion (M1, M2 or M4.1 stage) were eligible to participate in the study. A random sequence of 0 and 1 had already been prepared for every farm using the Random function in Microsoft Office Excel. Only cows that had not received any systemic analgesic or antibiotics for at least a week prior to enrolment were eligible to participate in the study. If the cow was undergoing any treatment with NSAIDs or antibiotics, it was automatically excluded from the experiment and the lesion was treated as per the farm's treatment protocol. Once a cow was deemed eligible (and only then) the printed randomisation list was used to determine whether it was placed in the control or treatment group. Cows with claw horn disruption lesions were not treated with NSAIDs on these farms and were not excluded from the study. The presence of claw horn disruption lesions (sole haemorrhage, sole ulceration and white line disease) was recorded and accounted for in multivariable regression analysis.

Cows in both groups were treated with topical application of an antibiotic spray containing oxytetracycline (Engemycin 25 mg/ml, MSD Animal Health) after the lesions had been carefully cleaned and dried with a clean paper towel. Animals in the treatment group also received an intramuscular injection of ketoprofen (3 mg/kg, Ketofen 10%; Ceva Animal Health) administered in the neck muscles. Treatments for each animal from both the control and the treatment group were

administered by one person, who also performed the lesion examination. The mobility score assessor was not involved in treating the cows but was responsible for updating the farm medical records for the treatment cows. Cows enrolled in the study were mobility scored again a week later. Since every farm was visited once weekly, the cows on the study were separated and mobility was scored by the same assessor alongside the cows selected for the main project. Rarely, due to changes of the routine for bank holidays or vacation, the assessor would visit the farms alone just to mobility score cows that had to be re-evaluated after the first week had passed or a substitute assessor would mobility score the enrolled cows. The mobility assessor did not have the animal records from the previous week when scoring them for the second week. In most instances, the assessor would also have to sort several other cows during the same session and therefore the possibility that the mobility scores post-treatment was biased is rather slim; however, an element of unconscious bias cannot be precluded with absolute certainty. Farm records such as calving date, parity and daily milk yield (for 1-week pre- and 1-week post-enrolment) were collected for all the cows enrolled in the study.

Statistical analysis

Data were analysed using JMP Pro 14 (SAS Institute Inc., Cary, NC). Univariable analysis was performed to evaluate the success of the randomisation process. The control and treatment groups were compared to detect differences in days in milk at enrolment, parity, mobility score at enrolment, mobility score assessor, average milk yield at enrolment, presence of sole ulceration, presence of white line disease, presence of sole haemorrhage and presence of DD stage M2. Analysis of variance was used for continuous outcomes. Chi-square tests were employed for binary or categorical outcomes.

Univariable analyses were undertaken between variables and the main outcome variables of interest before multivariable regression models were constructed. Parity was fitted in all models as a categorical variable with two levels (1 for primiparous and 2 for multiparous animals). Mobility scores were turned into a binary variable describing the prevalence of lameness (animals with a mobility score of 0 or 1 were classed as not lame (0) and animals with a mobility score of 2 or 3 were classed as lame[1]).

A multivariable logistic regression model with the presence of lameness (defined as a mobility score of 2 or 3) 1-week post-enrolment as an outcome was built. Explanatory variables originally offered in this model were: parity, stage of lactation (fresh, early or late lactation), presence of lameness at enrolment, assessor of mobility, treatment group, farm, presence of M2 stage DD lesion, presence of sole haemorrhage, presence of white line disease and presence of sole ulceration. Variables were removed from the model manually and in a stepwise manner (with the variable with the highest p-value removed at each step), and only variables with $p < 0.10$ (likelihood ratio test) were kept in the final model. Farm and treatment groups were kept in the model regardless of their p-value. The Lack of Fit test was used to evaluate models goodness of fit and the likelihood ratio test was used to determine the overall significance of the models. The predictive ability of the logistic regression model was assessed with receiver operating characteristic analysis and the calculated area under the curve. Results from logistic regression are presented as odds ratios. The p-values and 95% confidence intervals (CIs) for calculated odds ratios are Wald based estimates. All comparisons between different levels of categorical explanatory variables are for the odds of being lame versus the odds of not being lame 1-week post-enrolment.

A multivariable logistic regression model with the presence of lameness (defined as a mobility score of 2 or 3) 1-week post-enrolment as an outcome was also built including only animals that were lame at enrolment. Only 20 animals were available for this analysis. Explanatory variables originally offered in this model were: parity, stage of lactation (fresh, early or late lactation), presence of lameness at enrolment, assessor of mobility, treatment group, farm, presence of M2 stage DD lesion, presence of sole haemorrhage, presence of white line disease and presence of sole ulceration. Variables were removed from the model manually and in a stepwise manner (with the variable with the highest p-value removed at each step), and only variables with $p < 0.10$ (likelihood ratio test) were kept in the final model. Farm and treatment groups were kept in the model regardless of their p-value.

A multivariable linear regression model with average daily milk yield the week post enrolment as an outcome was also built. The following explanatory variables were originally offered to the model: parity, stage of lactation (fresh, early or late lactation), lameness at enrolment, average daily milk yield the week before enrolment, farm, presence of M2 stage lesion, presence of sole haemorrhage, presence of white line disease and presence of sole ulceration. The stage of lactation was combined with lameness at enrolment to create a new variable in the final model (stage of lactation by lameness at enrolment). Associations between explanatory variables were also investigated to identify collinearity between variables. Interaction terms of interest were also offered to this model (parity by treatment group and stage of lactation by lameness at enrolment by treatment group). Variables and their interactions were removed from the model manually and in a stepwise manner (with the variable with the highest p-value removed at each step), and only variables with $p < 0.10$ (F-test) were kept in the final model. Farm and treatment groups were included in all the models regardless of their p-values. If an interaction term was found to be significant, then the individual effects were kept in the final model whether they were significant or not. Rows with missing data were not included in the analysis. Residuals by model predicted values, student residuals, and residuals normal quantile plots were visualised in order to

TABLE 1 Summary data for the study population

		Treatment	Control	Enrolled	Lame
Enrolled animals	**Farm 1**	4	5	9	3
	Farm 2	7	1	8	1
	Farm 3	69	53	122	16
	Farm 4	10	9	19	1
	Parity group 1	21	19	40	
	Parity group 2	69	49	118	

	Farm 1	Farm 2	Farm 3	Farm 4
Daily milk yield at enrolment (kg/d) Average (range)	44.54 (35.9–47.9)	24.74 (6.3–36.86)	40.9 (20–65.5)	41 (7.4–64.7)

		Days in milk			
Stage of Lactation	***N***	**Mean**	**Min**	**Max**	**Std dev**
Fresh	34	6.56	1	16	2.94
Early	59	85.98	61	107	12.87
Late	65	185.55	170	221	11.91

Foot Lesions at enrolment	***N***	**% of total**
DD stage M2	84	53.16%
DD stage M1 or M4.1	74	46.83%
Sole ulcer	6	3.80%
White line disease	14	8.86%
Sole haemorrhage	3	1.9%

evaluate the model's goodness of fit and that assumptions of normality and homoscedasticity were met. Leverage plots (partial-regression residual leverage plots) for all fixed effects included in the model were also visualised. For categorical explanatory variables, results are presented as least squares means (adjusted means) ± standard error of the mean. Pairwise comparisons of least squares means were made using the Tukey-Kramer Honestly Significant Difference test.

RESULTS

One hundred and fifty-eight cows were enrolled in the study, 90 cows were enrolled in the treatment group and 68 were in the control group. Randomisation lists were prepared for each farm and for the approximate number of animals we were expecting to enrol in each farm. We ended up enrolling fewer animals due to COVID-19 restrictions and this led to unbalanced T and C groups in two farms. Had we been able to continue enrolling animals as originally planned, our groups would have been more balanced. Table 1 shows summary data for the study population. A total of 310 mobility scoring assessments were performed. Out of those assessments, 285 were performed by the main assessor of mobility in the project (C. Bedford) and 25 were performed by substitute assessors (M. Barden, $n = 7$; B. E. Griffiths, $n = 16$ and T. Menka, $n = 2$). Among the 158 animals that were enrolled a total of six were missed for the second mobility scoring assessment (Farm 1, $n = 1$; Farm 3, $n = 4$ and Farm 4, $n = 1$). This was a result of these animals not being sorted during the visit; no culling occurred the week following treatment.

Univariable statistical analyses performed to check the randomisation process found no statistically significant difference between the control and the treatment group with respect to parity, days in milk, milk yield at enrolment or daily milk yield the week before enrolment. Table 2 summarises all the univariable analyses that were performed in order to ensure that the randomisation process was successful. As previously mentioned, cows eligible for enrolment were at the fresh, early lactation or late lactation timepoints. No difference was found between the control and treatment groups regarding the distribution of the cows in the aforementioned time points. Lameness prevalence (defined as a mobility score of 2 or 3) within the control and treatment group was 11.8% and 14.4% respectively and not statistically different between the two groups. Likewise, the prevalence of sole ulcers, sole haemorrhage, white line disease, and the presence of M2 stage DD was not different between groups.

Univariable analysis showed that 12 out of 65 (18.46%) animals in the control group were lame at the second evaluation while 10 out of 87 (11.49%) animals in the treatment group were lame at the second evaluation ($p = 0.23$). A multivariable logistic regression model, using cows being lame or not at the second evaluation as the outcome variable, was undertaken; the main results from this model are presented in Table 3. Variables retained in this model (with p-values obtained for each variable from the final multivariable analysis) were: lameness at enrolment ($p < 0.001$), mobility score assessor ($p = 0.028$),

TABLE 2 Univariable analyses result to check for differences between the treatment and control group regarding parity, days in milk (DIM), stage of lactation, lameness, sole haemorrhage, sole ulcer, M2 stage digital dermatitis at enrolment, milk yield at enrolment, and mobility assessment. Parity group 1 refers to primiparous animals while group 2 refers to multiparous animals

Explanatory variable	Level	Control Group	Treatment group	*p*-value
Parity	1	27.94%	23.33%	0.51
	2	72.06%	76.67%	
Stage of lactation	Fresh	23.53%	20%	0.62
	Early lactation	39.71%	35.56%	
	Late lactation	36.77%	44.44%	
Sole haemorrhage at enrolment	0	97.06%	98.89%	0.41
	1	2.94%	1.11%	
Lameness at enrolment	0	88.24%	85.56%	0.62
	1	11.77%	14.44%	
Sole ulcer at enrolment	0	97.06%	95.56%	0.62
	1	2.94%	4.44%	
White line disease at enrolment	0	88.24%	93.33%	0.26
	1	11.76%	6.67%	
DD stage M2 at enrolment	0	45.59%	47.78%	0.79
	1	54.41%	52.22%	
DIM (±SD)	Fresh	6.37 ± 0.74	6.72 ± 0.70	0.73
	Early lactation	85.00 ± 2.49	86.81 ± 2.29	0.59
	Late lactation	184.84 ± 2.40	186.00 ± 1.90	0.71
Milk Yield (kg/d) at enrolment (±SD)		40.19 ± 12.28	40.63 ± 11.02	0.62

TABLE 3 Results from multivariable logistic regression model for outcome: Lameness 1-week post-enrolment. Presented odds ratios (OR) are for each level against the reference category for the odds of being lame (mobility score 2 or 3) 1-week post-enrolment; *p*-values and 95% confidence intervals (CI) are Wald based estimates

Explanatory variable	Level	Odds Ratio	95% CI	*p*-value
Lameness at enrolment	1	13.55	3.46–53.01	<0.001
	0	Reference		
Sole ulcer at enrolment	1	9.93	1.15–85.93	0.037
	0	Reference		
White line disease at enrolment	1	4.39	0.87–22.24	0.074
	0	Reference		
Treatment group	Control	2.57	0.82–8.01	0.103
	treatment	Reference		

the prevalence of white line disease at enrolment ($p = 0.088$), the prevalence of sole ulceration at enrolment ($p = 0.052$), treatment or control group ($p = 0.097$) and farm ($p = 0.258$). The odds of a cow being found lame at the second evaluation were 13.55 (95% CI: 3.46–53.01, $p < 0.001$) times higher for animals that were lame at enrolment compared to cows that were not lame at the time of enrolment. Animals that only received topical antibiotic treatment were at 2.57 (95% CI: 0.82–8.01, $p = 0.103$) times higher odds to be lame at the second evaluation compared to those that received ketoprofen as well. Cows diagnosed with sole ulceration or white line disease at the time of enrolment were at 9.93 (95% CI: 1.15–85.93, $p = 0.037$) and 4.39 (95% CI: 0.87–22.24, $p = 0.074$) times higher odds of being lame a week post enrolment comparing to cows not affected by these foot lesions.

When only lame at enrolment animals were considered, five out of seven (71.43%) lame animals that were in the control group remained lame a week after the treatment while four out 13 (30.77%) lame animals that were in the treatment group remained lame a week after treatment ($p = 0.08$, resulted from univariable analysis). Variables that were retained in the multivariable logistic regression model with lameness a week post-treatment as an outcome (only for animals that were also lame at enrolment) were: mobility score assessor at enrolment ($p = 0.092$), presence of sole ulceration at enrolment ($p = 0.091$), treatment or control group ($p = 0.011$) and farm ($p = 0.093$). Animals that only received topical antibiotic treatment were at 20.20 (95% CI: 1.40–291.28, $p = 0.027$) times higher odds to be lame at the second evaluation compared to those that received ketoprofen as well. These results should however be treated with caution as they are based on data from only 20 animals.

Variables retained in the model with average daily milk yield for the week post enrolment were: the average daily milk yield for the week before enrolment ($p < 0.001$), stage of lactation by lameness at enrolment ($p < 0.001$), treatment group ($p < 0.01$), stage of lactation by lameness at enrolment by treatment group ($p < 0.001$) and farm ($p = 0.65$). The main results from this model are presented in Table 4 and Figure 1. Cows that received ketoprofen did produce more milk per day the week after treatment than the cows in the control group with adjusted means (± standard error)

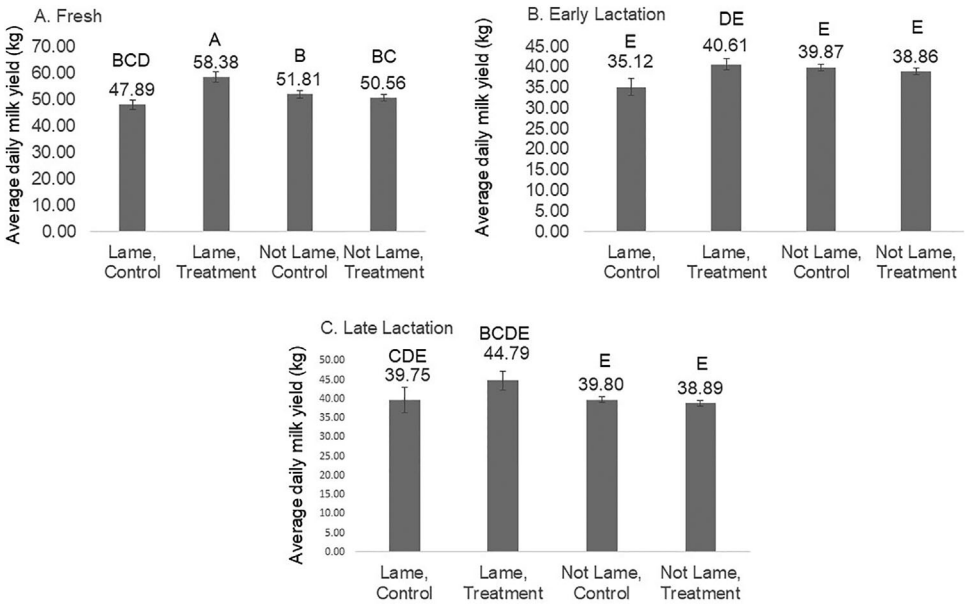

FIGURE 1 Results from multivariable linear regression model for outcome mean daily milk yield (kg) during the first-week post-enrolment for cows enrolled at different stages of lactation (Fresh (a), Early Lactation (b) or Late Lactation (c)). Adjusted means ± standard error of the mean presented here was obtained for the interaction term stage of lactation by lameness at enrolment by treatment group. Levels within a variable with different letters are statistically significantly different (honestly significant difference test. $p < 0.05$)

TABLE 4 Results from multivariable linear regression model for outcome mean daily milk yield (kg) during the first-week post-enrolment

Explanatory variable	Level	Adjusted means	Standard error	*p*-value
Treatment group	Control	42.37	0.87	<0.01
	Trt	45.35	0.71	
		Estimate		
Mean daily milk yield before enrolment	Continuous variable	0.97	0.04	<.0001

being 45.35 ± 0.71 and 42.37 ± 0.87 kg per day respectively ($p < 0.01$). The effect of ketoprofen administration was more prominent on cows that were freshly calved and lame at enrolment. These cows produced 58.38 ± 1.85 kg per day the week after treatment if they were in the ketoprofen treatment group comparing to the control ones that produced 47.89 ± 1.81 kg per day ($p < 0.05$).

DISCUSSION

Our study shows that administering ketoprofen when treating cows with DD may have beneficial effects on their mobility and their milk production especially if animals are visibly lame when treated. In a recent 'expert opinion' survey it was reported that nine out of 12 experts would recommend the use of NSAIDs for the treatment of active DD but most of them would reserve this for cows with a mobility score of 3.[12] Importantly, the decision regarding this matter could not be evidence-based as there has been no published study investigating this so far. Our study provides the first evidence of possible welfare and production benefits associated with the use of NSAIDs when treating active DD lesions.

Our study showed potential benefits of ketoprofen administration on animals' mobility 1-week post-treatment. The effect of treatment on lameness 1-week post-treatment was not statistically significant when the whole study population was considered ($p = 0.097$) but a numeric difference was observed. This effect was more prominent when only lame at enrolment animals were considered. Only 20 animals were included in this analysis and therefore results should be treated cautiously. A follow-up study focusing on enrolling more cows affected with DD and with a mobility score greater than 1 is warranted. Similar findings have been reported for lameness or non-infectious lameness causing lesions but this is the first time this is shown for DD lesions specifically. Previous studies have shown positive outcomes of administering ketoprofen in the treatment of claw horn lesions[14]; positive effects on animal behaviour were also shown.[17] Whay et al.[18] have also shown positive effects of ketoprofen administered to lame cows. Other studies that dealt with the use of NSAIDs, such as flunixin meglumine[19] and tolfenamic acid[20] in the treatment of lameness have shown contradicting results. Chapel et al.[19] did not report an effect of flunixin meglumine administration on cattle locomotion scores post trimming. Laven et al.[20] did show improvements in locomotion scores of lame cows treated with tolfenamic acid.

The pain generated by DD negatively affects the animals' behaviour and productivity,[21] both directly and indirectly through a decrease in dry matter intake. It has been shown that lame cattle consume less feed and produce less milk than their non-lame counterparts.[22] The consumption of sufficient amounts of dry matter is particularly important for periparturient animals. If cows develop DD and, even

more importantly, become lame in the periparturient period they will suffer production loss possibly due to reduced dry matter intakes.[23] We believe that at this last point lies the reason why the administration of ketoprofen had such a significant effect on the milk production of the DD affected, lame animals, especially for freshly calved animals. On the basis that the treatment of DD should also have a focus on limiting production losses, the administration of ketoprofen appears very promising. The potential welfare benefits could be enough to justify the use of ketoprofen. However, the possible milk production benefits may also offer economic benefits to the farmer (especially given the fact that administration of ketoprofen does not require a milk withdrawal period in the UK) and therefore may make it more likely for such a treatment approach to be adopted. It should however be noted that a comprehensive cost-benefit analysis was beyond the scope of our study.

Our study has limitations that should be taken into consideration when interpreting its findings. As already stated in the materials and methods section, the researcher performing mobility scoring did not administer treatments but was responsible for updating farmers' records and therefore may not be considered entirely masked to treatment when performing mobility scoring 1-week post-enrolment. However, given the fact that mobility scoring was happening one week later and while sorting a large number of cows for a different project we believe that the chances this scorer would actually remember certain cows and their treatment are very low. In any case, this potential issue could not have affected the results associated with milk production. Another possible study limitation is the fact that some of the enrolled cows were affected by DD and sole ulceration or white line disease. Ketoprofen effects for these animals could be associated with the presence of these other lesions. The presence of sole ulceration or white line disease was included in our multivariable analysis and therefore the treatment effect we describe in this model was corrected for the effects of these lesions. Furthermore, we did run our analysis excluding cows with sole ulceration and white line disease and still obtained very similar results. Due to the way this study was run we were unable to administer a three-day course of ketoprofen and were only able to perform one mobility scoring a week post-treatment. Potential benefits of ketoprofen administration could have been better realised had we been able to administer more than one dose and monitor animals more intensively. Finally, based on initial planning (based on the number of animals enrolled in the main project and our existing knowledge of active DD incidence rates on the collaborating farms), we were aiming to enrol at least 250 animals in this study. Due to the COVID-19 pandemic breaking out while the study was ongoing, visits to the farms had to be halted. This resulted in the reduction of our sample size to 158 animals. This is still an acceptable sample size and did allow us to detect statistically significant differences (results regarding daily milk yield); however, a larger sample size would have increased the power of our study. This also led to the treatment and control groups being unbalanced which is another limitation that needs to be considered.

CONCLUSION

This randomised positively controlled clinical trial suggests that the addition of ketoprofen in the treatment of active DD lesions may be beneficial for animal welfare as it was associated with an improvement in mobility scores and for animal productivity as it was associated with an increased daily milk production (at least for the first few days post-treatment).

ETHICS STATEMENT

The study was conducted following ethical approval from the University of Liverpool Veterinary Research Ethics Committee.

CONFLICT OF INTEREST

KK, AA, CB, TM, MB, BEG, VSM and GO declare that they have no competing interests. DA and KT work for CEVA Animal Health that funded this study and is distributing Ketofen (the drug tested in this clinical trial). They were involved in discussions regarding study design and approved the final version of the manuscript but were not involved in data collection and analysis.

AUTHOR CONTRIBUTIONS

KK collected field data, assisted data analysis and co-wrote the first draft of the manuscript, AA collected field data and co-wrote the first draft of the manuscript, CB collected field data, TM assisted field data collection, MB assisted field data collection, BEG assisted field data collection, DA offered advised regarding study design, KT offered advised regarding study design, VSM performed statistical analyses, AC offered advised regarding study design and GO (corresponding author) designed and supervised the study and assisted with the statistical analysis. All authors critically evaluated the manuscript and approved the submitted version.

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CEVA Animal Health Ltd provided funding and the ketoprofen used for the trial. There was no award/grant number associated with this project. The funder was involved in discussions regarding study design and approved the final version of the manuscript but was not involved in data collection and analysis.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available at reasonable request.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vetr.977.

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REFERENCES

1. Huxley JN. Impact of lameness and claw lesions in cows on health and production. Livestock Sci. 2013;156(1–3):64–70.
2. Amory JR, Barker ZE, Wright JL, Mason SA, Blowey RW, Green LE. Associations between sole ulcer, white line disease and digital dermatitis and the milk yield of 1824 dairy cows on 30 dairy cow farms in England and Wales from February 2003-November 2004. Prev Vet Med. 2008;83(3–4):381–91.
3. Buch LH, Sørensen C, Lassen J, Berg P, Eriksson J-Å, Jakobsen JH, et al. Hygiene-related and feed-related hoof diseases show different patterns of genetic correlations to clinical mastitis and female fertility. J Dairy Sci. 2011;94(3):1540–51.
4. Solano L, Barkema HW, Mason S, Pajor EA, LeBlanc SJ, Orsel K. Prevalence and distribution of foot lesions in dairy cattle in Alberta, Canada. J Dairy Sci. 2016;99(8):6828–41.
5. Dippel S, Dolezal M, Brenninkmeyer C, Brinkmann J, March S, Knierim U, et al. Risk factors for lameness in freestall-housed dairy cows across two breeds, farming systems, and countries. J Dairy Sci. 2009;92(11):5476–86.
6. Cook NB. Prevalence of lameness among dairy cattle in Wisconsin as a function of housing type and stall surface. J Am Vet Med Assoc. 2003;223(9):1324–8.
7. Griffiths BE, Grove White D, Oikonomou G. A cross-sectional study into the prevalence of dairy cattle lameness and associated herd-level risk factors in England and Wales. Front Vet Sci. 2018;5:1–8.
8. Read DH, Walker RL. Papillomatous digital dermatitis (footwarts) in California dairy cattle: clinical and gross pathologic findings. J Vet Diagnostic Investig. 1998;10(1):67–76.
9. Krull AC, Shearer JK, Gorden PJ, Scott HM, Plummer PJ. Digital dermatitis: natural lesion progression and regression in Holstein dairy cattle over 3 years. J Dairy Sci. 2016;
10. Berry SL, Read DH, Famula TR, Mongini A, Döpfer D. Long-term observations on the dynamics of bovine digital dermatitis lesions on a California dairy after topical treatment with lincomycin HCl. Vet J. 2012;193(3):654–8.
11. Evans NJ, Murray RD, Carter SD. Bovine digital dermatitis: current concepts from laboratory to farm. Vet J. 2016;211:3–13.
12. Bird KL, Higgins H. Expert opinion on the treatment of individual cattle with digital dermatitis lesions. Cattle Pract. 2018;26(2):143.
13. Paudyal S, Manriquez D, Velasquez A, Shearer JK, Plummer PJ, Melendez P, et al. Efficacy of non-antibiotic treatment options for digital dermatitis on an organic dairy farm. Vet J. 2020;255:105417.
14. Thomas HJ, Miguel-Pacheco GG, Bollard NJ, Archer SC, Bell NJ, Mason C, et al. Evaluation of treatments for claw horn lesions in dairy cows in a randomized controlled trial. J Dairy Sci. 2015;98(7):4477–86.
15. Thomas HJ, Remnant JG, Bollard NJ, Burrows A, Whay HR, Bell NJ, et al. Recovery of chronically lame dairy cows following treatment for claw horn lesions: a randomised controlled trial. Vet Rec. 2016;178:116.
16. Whay HR, Main DC, Green LE, Webster AJ. Assessment of the welfare of dairy cattle using animal-based measurements: direct observations and investigation of farm records. Vet Rec. 2003;153(7):197–202.
17. Miguel-Pacheco GG, Thomas HJ, Kaler J, Craigon J, Huxley JN. Effects of lameness treatment for claw horn lesions on lying behaviour in dairy cows. Appl Anim Behav Sci. 2016;179:11–6.
18. Whay HR, Webster AJF, Waterman-Pearson AE. Role of ketoprofen in the modulation of hyperalgesia associated with lameness in dairy cattle. Vet Rec. 2005;157(23):729–33.
19. Chapel NM, Young JM, Wagner SA. The effects of flunixin meglumine and hoof trimming on lying behavior, locomotion, and milk production in lame and nonlame lactating dairy cows. J Dairy Sci. 2020;103(6):5422–30.
20. Laven RA, Lawrence KE, Weston JF, Dowson KR, Stafford KJ. Assessment of the duration of the pain response associated with lameness in dairy cows, and the influence of treatment. N Z Vet J. 2008;56(5):210–7.
21. Pavlenko A, Bergsten C, Ekesbo I, Kaart T, Aland A, Lidfors L. Influence of digital dermatitis and sole ulcer on dairy cow behaviour and milk production. Animal 2011;5(8):1259–69.
22. Galindo F, Broom DM. The effects of lameness on social and individual behavior of dairy cows. J Appl Anim Welf Sci. 2002;5(3):193–201.
23. Gomez A, Cook NB, Socha MT, Döpfer D. First-lactation performance in cows affected by digital dermatitis during the rearing period. J Dairy Sci. 2015;98(7):4487–98.

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