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Article Title: A randomised factorial design clinical trial to investigate the impact of parenteral long acting oxytetracycline, foot trimming and flunixine meglumine on time to recovery from lameness and foot lesions in sheep lame with footrot

Year of publication: in press

Link to published version:
http://www.wiley.com/bw/journal.asp?ref=0891-6640&site=1

Publisher statement: This is the pre-peer-reviewed version of the following article: Kaler, J.. et al. A randomised factorial design clinical trial to investigate the impact of parenteral long acting oxytetracycline, foot trimming and flunixine meglumine on time to recovery from lameness and foot lesions in sheep lame with footrot. Journal of Veterinary Internal Medicine, which will be published in final form at http://www.wiley.com/bw/journal.asp?ref=0891-6640&site=1

Randomised clinical trial of long acting oxytetracycline, foot trimming and flunixine meglumine on time to recovery in sheep with footrot

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Short title: Treatment for footrot

Keywords: Ovine, infectious disease, *Dichelobacter nodosus*, antibacterials

Abbreviations: NSAID, Non steroidal anti-inflammatory drug; OR, Odds Ratio

The trial was carried out on a commercial farm in England under supervision of researchers from University of Warwick, UK.

The study was supported by funds from the Biotechnology and Biological Sciences Research Council BBE01870X1.

Acknowledgements: We thank the farmer for help and Graham Medley for discussion.

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Abstract

Background: Internationally, foot trimming is used by most farmers and parenteral antibacterials by some, to treat sheep with footrot. Non steroidal anti-inflammatory drugs (NSAID) are sometimes used. No clinical trials have compared these treatments.

Objectives: To investigate the above treatments on time to recovery from lameness and foot lesions in sheep with footrot.

Animals: 53 sheep with footrot on a commercial farm in England.

Methods: In a randomised factorial design, the sheep were allocated to 6 treatment groups. The treatments were oxytetracycline spray to all sheep (positive control) and one or more of: parenteral administration of long acting oxytetracycline, flunixine meglumine and foot trimming on day 1 or day 6 of diagnosis. Follow-up was for 15 days. Time to recovery from lameness and lesions was investigated with discrete- time survival models.

Results: There was significant association ($p<0.05$) between recovery from lameness and lesions. Sheep receiving antibacterials parenterally recovered faster from lameness (odds ratio (OR): 4.92 (1.20-20.10)) and lesions (OR: 5.11 (1.16-22.4)) than positive controls whereas sheep foot trimmed on day 1 (lameness- OR: 0.05 (0.005-0.51); lesions- OR: 0.06 (0.008-0.45)) or day 6 of diagnosis (lameness-OR: 0.07 (0.01-0.72); lesions- OR: 0.07 (0.01-0.56)) recovered slowly than positive controls. NSAID had no significant effect on recovery.

Conclusions and Clinical Importance: If foot trimming on day 1 or 6 of diagnosis was stopped and parenteral antibacterials were used, then over 1 million sheep/annum lame with footrot in the UK, would recover more rapidly with benefits to productivity. Globally, this figure would be much higher.

Introduction

Footrot causes lameness in sheep throughout the world and is an important health, welfare and economic concern. Over 90% of flocks in the UK have lame sheep, with a within flock prevalence of ~ 10% [1, 2]. Warm, wet environmental conditions favour the spread of footrot[3] and the severity of clinical presentation. Virulent footrot presents clinically[3] with separation of hoof horn from the sensitive dermis with a characteristic smell [4]. It causes approximately 30%, and interdigital dermatitis (often benign footrot[5]) 50 – 60%, of lameness in sheep in the UK[2]. Benign and virulent footrot are caused by *Dichelobacter nodosus*. Over 95% of isolates of *D. nodosus* from the UK are virulent by laboratory tests[5], irrespective of serogroup and clinical presentation. Laboratory diagnosis is of limited value to diagnose individuals because culture and PCR give false positive and negative results. It is used to determine flock infection and control in countries where there are control policies whereas elsewhere clinical presentation is used.

Treatments for footrot include one or more of: trimming hoof horn, parenteral antibacterials and topical bactericide [6, 7]. The most popular treatment for footrot is trimming and applying a topical bactericide, with more than 90% farmers in the UK using this treatment in 2000[8] and 2004[9]. Trimming removes excess horn and exposes footrot lesions to air [7, 10]; 'letting air in' was recommended to combat *D. nodosus* because of its anaerobic nature[6, 11]. Some practitioners propose severe trimming of the hoof horn at diagnosis[12], however, many have moved away from this and recommend that hoof horn is trimmed carefully 5 days after treatment, when the lesions have start to heal[7, 13], there is no evidence for or against this latter recommendation. All foot trimming runs the risk of damaging the sensitive dermis of the foot, causing pain and granulomatous proliferations[3, 7].

In the UK, two epidemiological studies led to the hypothesis that parenteral and topical antibacterials were the most effective treatment for footrot [8, 14]. From clinical trials in Australia and the UK ~ 90% sheep were cured after treatment with penicillin and streptomycin[15], lincomycin and lincospectin[16], erythromycin[17] and long acting oxytetracycline[18,19]. However, in these trials no observations were made on lameness, only lesions, and all sheep were examined for the first time 4-5 weeks after treatment so there is no estimate of time to recovery. Foot trimming was combined with all treatments so the impact of trimming on recovery was not elucidated. Some farmers treat lame sheep with NSAID which have anti-inflammatory, anti-pyretic and analgesic properties that provide symptomatic relief from inflammatory conditions[20, 21]; their efficacy has not been evaluated.

There is no clinical trial that compares all treatments under similar conditions. The aim of the current study was to investigate the effects of long acting parenteral oxytetracycline, foot trimming on the same day or day 6 of diagnosis and flunixin meglumine (NSAID) on the time to recovery from lameness and foot lesions in sheep lame with footrot.

Materials and Methods

Study design

A randomised factorial-design clinical trial was conducted on a farm in England, with a history of sheep with footrot between October and December 2007. The flock comprised 250, 9-month-old ewes that were out-wintered and not pregnant. The farmer put three replicates of 18, 32 and 10 lame sheep into a field on 18/10/2007, 14/11/2007 and 5/12/2007 respectively. The lame sheep were identified with an ear tag and their locomotion[22] was scored by researchers. The feet were inspected and sheep with footrot (separation of the hoof horn and a characteristic smell) were recruited into the trial. The severity of lesions on each foot was recorded[23]. These sheep were lame for up to 2 weeks before they were recruited in the trial. Sheep lame for any other reason were treated using recommended treatments [7] and returned to the main flock.

Allocation to treatment groups

The 53 sheep (replicate 1=14, replicate 2=29, and replicate 3=10) were matched by maximum lesion severity and randomly allocated to one of six treatments (Table 1) by selecting a coloured ball from a bag. The treatments were antibacterial aerosol spray to all sheep and then parenteral administration of antibacterials on day 1 of diagnosis (n=34), NSAID on day 1 of diagnosis (n=8), foot trimming on day 1 (n=15) and foot trimming on day 6 (n=21) of diagnosis in an incomplete factorial design[24, 25]. The experimental protocol was approved by the Home Office as a comparison of currently used methods to treat footrot and therefore ethically acceptable. The researchers and farmer also discussed the treatments and the farmer approved them for his sheep.

The parenteral antibacterial was a long acting preparation of oxytetracycline[a] (200mg/ml) at a dose of 1ml/10kg bodyweight by deep intramuscular injection with a maximum dose of 5ml per site. The aerosol spray was terramycin[b] (oxytetracycline hydrochloride PhEur (3.93% w/w). The NSAID used was flunixin meglumine BP[c] at a dose of 2ml/45kg by intramuscular injection. Sheep were diagnosed and treated by two researchers (SLSD and JLW) trained by JK. All foot trimming was done by the farmer who was blinded to the treatment allocation. This farmer had been sheep farming for 15 years and did not trim feet severely when he trimmed them (observations of SLSD and JLW). All selected sheep on day 1 and only sheep still lame on day 6 of diagnosis allocated to be trimmed were foot trimmed.

Follow up

Sheep locomotion was scored[22] and their feet inspected and lesions scored on three occasions each week for up to 15 days. All sheep not returning to locomotion score zero by 15 days were inspected and those with footrot or interdigital dermatitis were treated with parenteral antibacterials and antibacterial spray.

Statistical analysis

Outcome and model set up

Data were stored in Microsoft Access. The outcomes of interest were time to recovery from lameness and time to recovery from footrot lesions. A sheep was defined as recovered from lameness when it had a locomotion score of zero for two consecutive observations. Recovery from footrot lesions occurred when the lesion had healed and there was no foul smell or exudates. Discrete time survival analysis[26] modelling hazard probability for recovery was used to analyse the data[d]. For both lameness and lesions the time to recovery was divided into three discrete-time periods 1-5 days (T_1), 6-10 days (T_2) and 11-15 days (T_3) and sheep either recovered or not in each time period. The hazard probability is the conditional probability that an event occurs in a particular time period, given that it has not occurred in the previous time period (s) and is described by an odds ratio.

Data were converted into sheep-period format with a separate record for each discrete time that a sheep had a probability of recovering. For each of these time periods a binary variable was used to indicate whether recovery occurred or not. Sheep were excluded from all subsequent time periods once they had recovered and those not recovered by 15 days were right censored.

The model took the form[26]:

$$\text{logit } h(T_{it}) = [\alpha_1 T_{1it} + \alpha_2 T_{2it} + \alpha_3 T_{3it}] + [\beta_1 X_{1it} + \beta_2 X_{2it} \ldots\ldots + \beta_P X_{Pit}]$$

Predictor variables

The predictor variables were discrete time periods ($T_{1,}$ $T_{2,}$ T_3) , did or did not receive parenteral administration of antibacterial or NSAID on day 1 of diagnosis, the time dependent variable no foot trimming, foot trim on day 1 or day 6 of diagnosis, with a positive control of receiving topical antibacterials (Table 2), locomotion score at the start of the trial (locomotion score ≤ 2 or 3), number of feet affected with footrot (1 or 2), replicate (1, 2 or 3) and severity of footrot lesions (score 1 or 2). Interactions between the variables were investigated. Observations that clustered within sheep were included as a random effect.

The adjusted odds ratio (OR) (the hazard probability ratio) and associated 95% confidence intervals were estimated. The model fit was evaluated by examining the deviance residuals at sheep-period level and the sum of squared deviance residuals for each sheep's contribution to the deviance statistic [26]. The association between recovery from lameness and healing of footrot lesions was assessed using a χ^2 test for each time period. The predicted probability for recovery from lameness and footrot lesions in the discrete time period was plotted.

Results

On day 1 of diagnosis, 1 sheep had a locomotion score 1, 19 a score 2 and 33 had a locomotion score 3. Sixty eight percent of sheep (36/53) had one foot affected with footrot and 32% (17) had two feet affected and 60% (32) had a footrot severity score 1 and 40% (21) had a severity score 2. The environmental conditions were fairly similar for each replicate; temperatures ranged from 7 to 11° C with a rainfall of 45 to 50 mm during the trial[27]. Sheep were moved straight to pasture after treatment, the weather was mostly dry for the 24 hours after treatment but moisture levels due to dew are unknown. The proportion of sheep allocated to each treatment in each replicate was similar (Table 2).

Approximately 51% (27/53) of sheep recovered from lameness during T_1, 55% (14/26) during T_2 and 58% (7/12) during T_3. The time to recovery from lameness and lesions was significantly associated ($p<0.05$). Lameness and foot lesions resolved in the same time period except for 4 and 1 sheep that were still lame at the end of T_1 and T_2 respectively but had no lesions; these sheep recovered from lameness in the following time period. Recovery rates were not significantly different between the three discrete time periods (Table 3). Five sheep were still lame and had lesions at the end of T_3; all had been foot trimmed, one had been treated with parenteral antibacterials.

Sixty-five percent (22/34) of sheep that received antibacterials administered parenterally recovered from lameness and 76% (26/34) from lesions in $T_{1.}$ Nine of the remaining 12 sheep and 5 / 8 sheep with lesions, recovered from lameness and lesions respectively in T_2. Only 26% (5/19) of sheep that did not receive parenteral administration of antibacterials recovered from both lameness and lesions in T_1 and a further 36% (5/14) and 43% (6/14) recovered from lameness and lesions respectively in T_2. Sheep that received parenterally administered antibacterials were significantly more likely to have a faster recovery from both lameness (OR: 4.92 (1.20-20.10)) and lesions (OR: 5.11 (1.16-22.40)) than positive controls. There was no significant effect of NSAID on the time to recovery from lameness (Table 3).

Four out of 15 trimmed sheep recovered from lameness and 5/15 from lesions in $T_{1.}$ There were 12 sheep that were still lame by day 6 of diagnosis that were foot trimmed, 3/12 recovered from both lameness and lesions in T_2. Sheep that were trimmed on day 1 (lameness - OR: 0.05 (0.005-0.51); footrot lesions- OR: 0.06 (0.008-0.45)) or day 6 (lameness- OR: 0.07 (0.01-0.72); footrot lesions- OR: 0.07 (0.01-0.56)) of diagnosis were significantly less likely to recover in the time period than sheep that were not trimmed (Table 3).

The overall estimated hazard probability for recovery from both lameness and lesions within 5 days of treatment was highest in sheep that were treated with parenterally administered aantibacterials without foot trimming (Figure 1) followed by positive controls and sheep that were foot trimmed and given parenteral administration of antibacterials and was lowest in sheep that were foot trimmed and not given parenteral administration of antibacterials.

Sheep with a locomotion score 3 took longer to recover from lameness (OR: 0.05 (0.01-0.24)) and lesions (OR: 0.04 (0.007-0.21)) than sheep with locomotion score ≤ 2. There was no significant effect of number of feet affected or severity of footrot lesions or replicate on the time to recovery from lameness or lesions (Table 3).

There were no statistically significant interactions between treatments. The models provided a reasonable fit to the data (Hosmer–Lemeshow statistic, lameness (p=0.93), lesions (p=0.52)). There were no extreme observations with large residuals in the index plots of deviance residuals.

Discussion

In this trial sheep treated with parenteral administration of long acting oxytetracycline (together with an oxytetracycline spray) were significantly more likely to recover from footrot lesions and lameness within 5 days of treatment compared with sheep that were foot trimmed with or without parenteral administration of antibacterials or positive controls (Table 3). The explanation for this rapid response to treatment might be that *D. nodosus* is a bacterium susceptible to all antibacterial classes and that the antibacterials administered parenterally penetrated deep into the dermis where *D. nodosus* can be present [15]. The results fit with the cure percents for parenteral administration of antibacterials from other studies but we recorded time to recovery from both lameness and lesions which was rapid. The results from the current study suggest that parenteral administration of antibacterials is very effective (with 75% sheep recovering within 5 days) in minimising the time that sheep are lame and thus treating all lame sheep with footrot with them could not only improve the health and welfare of the sheep but could also minimise the effects of chronic lameness on loss of body condition and reduced productivity, such as lambs born and lamb growth rate [28] .

Sheep in the current study were moved straight to pasture after treatment with parenteral antibacterials. Previous evidence suggests that a dry environment for 24 hrs after parenteral treatment is important [15] for improved efficacy of short acting parenteral antibacterials. Thus it is possible that for long acting preparations with therapeutic levels present in serum for at least 72 hours [29] , provision of a dry environment for up to 24 hrs is not be essential, especially considering that the majority of sheep recovered within 5 days of treatment.

Foot trimming sheep lame with footrot without administration of antibacterials parenterally was associated with the longest time to recovery from lameness and lesions both when sheep were trimmed on day 1 or day 6 of diagnosis, suggesting that foot trimming lame sheep had a detrimental effect on recovery whether the lesions were active or healing. For discrete time model the odds of recovery from lameness or lesions within each 5 day period were similar for sheep trimmed on day 1 or day 6 of diagnosis, suggesting that time of trimming did alter the time to recovery differentially. In addition, lame sheep trimmed on day 6 of diagnosis were compared to sheep still lame at day 6, avoiding selection bias. Trimmed sheep were lame and had lesions for twice as long as the non-trimmed sheep, and presumably were infectious for twice as long, if we assume that infectiousness is correlated with the presence of lesions. The delay in recovery among trimmed sheep might be because trimming the hoof horn aggravated the foot and delayed healing because of physical damage to the foot. The farmer did not trim feet severely and it is not unreasonable to assume that his trimming practice is similar to other farmers who trim feet without causing them to bleed. It is quite possible that had there been 'severe' trimming and damage to the dermis that the time to recovery might have been longer.

The combination of antibacterials administered parenterally, foot trimming and foot spraying had a similar time to recovery from lameness and lesions as antibacterial spray alone, suggesting that parenteral administration of an antibacterial agent negated the negative effect of foot trimming but did not lead to as rapid a recovery from lameness as these antibacterials without foot trimming. Quite remarkably, sheep that were not foot trimmed and did not receive parenteral antibacterials, but only an oxytetracycline spray (as were all sheep in this study) recovered more quickly than those foot trimmed and given topical spray (Figure 1), suggesting that foot trimming cannot be recommended as a 'second best' treatment where farmers do not wish to use antibacterials administered parenterally but rather it is detrimental to recovery from lameness and lesions.

In the current study, sheep with a higher locomotion score at the start of the study took longer to recover, suggesting an association between the severity of lameness and time to recovery from footrot lesions and lameness. There was no significant association between the severity of the initial lesion (even in univariate analysis) and the time to recovery from lesions or lameness, also reported elsewhere [17, 19.] . It is possible that the classification of under-run area (Table 3) was insufficient to detect a difference or that the sheep rate of healing is such that severe lesions heal as rapidly as mild lesions. A positive association between presence of lesions and lameness was also observed in a longitudinal study[9]. We hypothesise that lesions cause lameness. Consequently, sheep with old and chronic lesions and / or extensive damage to the wall horn might take longer to recover from lameness if the lesions take longer to heal. However in an intervention study[23] sheep lame for several months after treatment with parenteral antibacterials recovered in median time of 4 days. This might suggest that given appropriate treatment the propensity for the sheep foot to heal is great.

The lack of association between the number of feet with footrot and time to recovery from footrot contrasts with a previous study [19] where sheep with 1 or 2 feet affected had higher cure rates than sheep with 3 or 4 feet affected. However, because sheep had a maximum of two feet affected in the current study it was not possible to investigate the relationship between more than this number of affected feet and recovery.

NSAID did not change the time to recovery from lameness significantly, possibly because 8 sheep received NSAIDS or because they were given for only one day. A previous study [30] suggested that after 3-days administration of flunixine meglumine noxious mechanical stimulation to sheep with footrot responses were comparable to healthy sheep. NSAID do produce analgesia for up to 24 hrs and so one injection might help ewes to continue to feed and allow their lambs to feed, it certainly should not be discounted because of the results from the current study.

No non-lame sheep were foot trimmed in this study and it is only possible to hypothesise on the impact of routine foot trimming from other studies [8, 14, 31] where trimming was positively correlated to lameness. Foot trimming might cause damage to the foot and spread or increase susceptibility to *D. nodosus* or it might be indirectly causal if farmers trim rather than treat lame sheep [32]. Untreated sheep with footrot can remain lame for many months.

This study is an example of reduction and refinement in use of animals in experiments. A factorial design comparing the effects of several treatments individually and in combination used a relatively small number of sheep (53) with sufficient power, possibly with the exception of NSAID. In the absence of a gold standard laboratory test, sheep were diagnosed using characteristic clinical presentation. The researchers were not blinded to treatment allocation which could lead to bias, however, during follow up, sheep number was used to identify individual animals and it seems unlikely that researchers remembered the identity of a sheep and its treatment. The use of one flock and one environment gave consistency to compare the effectiveness of the treatments and avoided confounding factors such as differences in breed, age, micro and macro environment and other factors [19] that vary between farms. Further studies are required to externally validate these findings and to investigate the effect of trimming feet of non-lame sheep.

Footnotes

[a] Intervet/ Schering-Plough Animal Health, UK

[b] Pfizer Limited, UK

[c] Intervet/ Schering-Plough Animal Health, UK

[d] Stata 10.0, Statacorp, USA

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Table 1: Number of sheep and treatment given in the factorial design

	Parenteral antibacterial at day 1 of diagnosis	Foot trimming at day 1 of diagnosis	Foot trimming at day 6 of diagnosis	Non steroidal anti-inflammatory drug at day 1 of diagnosis
Treatment group 1 (n=9)	9	0	0	0
Treatment group 2 (n=8)	8	0	0	8
Treatment group 3 (n=7)	7	7	0	0
Treatment group 4 (n=10)	10	0	10*	0
Treatment group 5 (n=8)	0	8	0	0
Treatment group 6 (n=11)	0	0	11*	0
Total (n=53)	34	15	21	8

* 5 lame sheep from Treatment group 4 and 7 lame sheep from Treatment group 6 were trimmed because 5 and 4 sheep from these groups recovered before day 6 respectively.

Table 2: Distribution of sheep in treatment groups by replicate and footrot severity

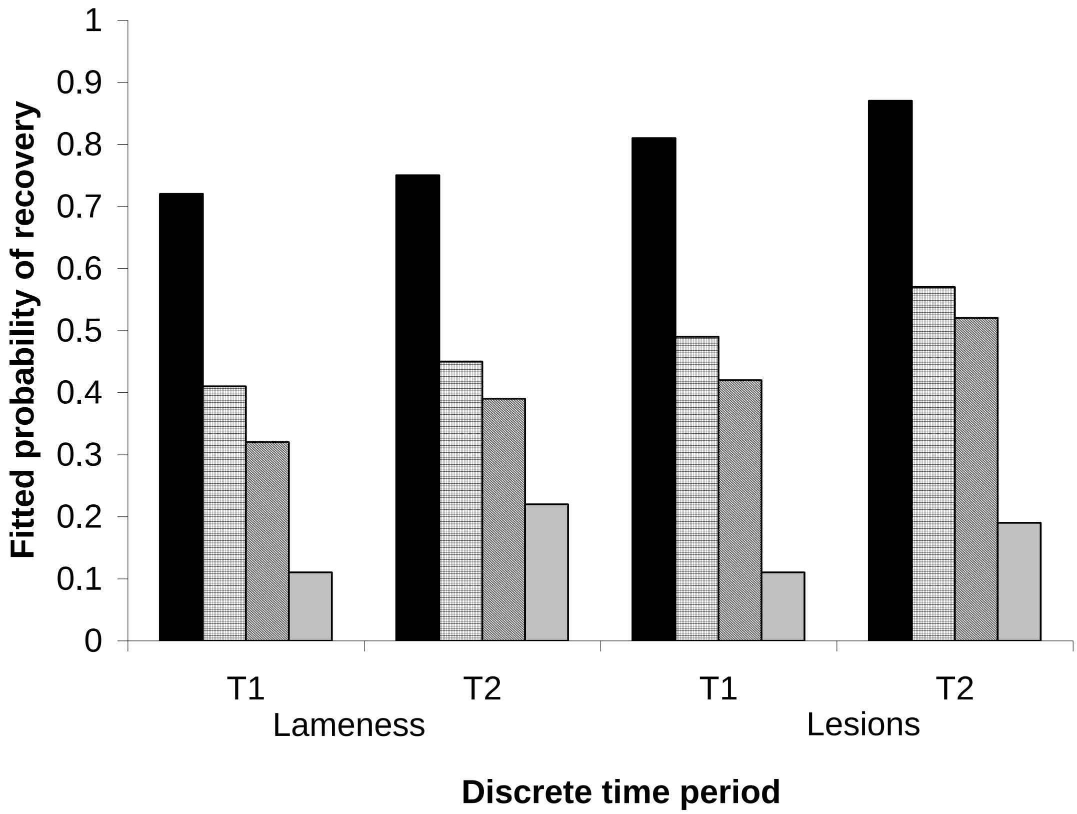
	Replicate 1		Replicate 2		Replicate 3		Footrot severity score 1		Footrot severity score 2	
Treatment Group	Number of sheep	Percent (%)	Number of sheep	Percent (%)	Number of sheep	Percent (%)	Number of sheep	Percent (%)	Number of sheep	Percent (%)
1	2	14.3	5	17.2	2	20.0	5	15.6	4	19.0
2	2	14.3	5	17.2	1	10.0	5	15.6	3	14.3
3	2	14.3	4	13.8	1	10.0	4	12.5	3	14.3
4	3	21.4	5	17.2	2	20.0	6	18.8	4	19.0
5	2	14.3	4	13.8	2	20.0	5	15.6	3	14.3
6	3	21.4	6	20.7	2	20.0	7	21.9	4	19.0
Total	14	100.0	29	100.0	10	100.0	32	100.0	21	100.0

Table 3: Multivariable discrete time survival analysis of time to recovery from lameness and footrot lesions of 53 sheep with footrot after treatment with combinations of parenteral long acting oxytetracycline at day 1 of diagnosis, NSAID at day 1 of diagnosis and foot trimming at day 1 or day 6 of diagnosis

Predictor Variable	Lameness				Footrot lesions			
	No. of sheep obs.	OR	95% C.I.	p-value	No. of sheep obs.	OR	95% C.I.	p-value
T_3 (time period 3)	12	Ref.			11	Ref.		
T_1 (time period 1)	53	0.28	0.04-1.98	0.20	53	0.15	0.02-1.31	0.09
T_2 (time period 2)	26	1.71	0.26-11.04	0.57	22	0.71	0.08-6.11	0.75
Parenteral LAO at day 1 of diagnosis- No	42	Ref.			41	Ref.		
Yes	49	4.92	1.20-20.1	0.02	45	5.11	1.16-22.4	0.03
NSAID at day 1 of diagnosis-No	81	Ref.			78	^		
Yes	10	1.64	0.28-9.57	0.57	8			
Foot Trimming at day 1 of diagnosis - No	76	Ref.			71	Ref.		
Yes	15	0.05	0.005-0.51	0.003	15	0.06	0.008-0.45	0.006
Foot Trimming at day 6 of diagnosis- No	79	Ref.			74	Ref.		
Yes	12	0.07	0.01-0.72	0.009	12	0.07	0.01-0.56	0.01
Locomotion score at the start of the trial= ≤ 2#	26	Ref.			25	Ref.		
Locomotion score at the start of the trial= 3##	65	0.05	0.01-0.24	<0.001	61	0.04	0.007-0.21	<0.001
No. of feet affected =1	59	Ref.			56	Ref.		
No. of feet affected =2	32	0.84	0.24-2.93	0.79	30	0.84	0.26-2.65	0.77
Replicate 1	20	Ref.			20	Ref.		
Replicate 2	47	0.71	0.16-3.09	0.65	43	0.92	0.26-3.21	0.90
Replicate 3	24	0.43	0.08-2.05	0.28	23	0.67	0.18-2.51	0.56
Footrot severity score 1*	53	Ref.			50	Ref.		
Footrot severity score 2**	38	1.28	0.38-4.27	0.68	36	0.83	0..21-3.24	0.80

LAO, long acting oxytetracycline; OR, odds ratio; obs., observations; Ref., reference; # ,Visible nodding of head in time with short stride and/or uneven posture, shortened stride on one leg; ## ,Uneven posture, shortened stride on one leg, excessive flicking of head more than nodding in time with short stride; *,<50% of heel/sole/wall separation;**,≥50% and <100% heel/sole/wall separation; ^ coefficient could not be estimated because all sheep recovered in T_1

Figure 1: The fitted hazard probability of recovery from lameness and footrot lesions within 5 days when treated with or without a parenteral antibacterial injection with no foot trimming or foot trimming at discrete times T1 and T2



Black bar: parenteral antibacterial and no foot trimming; White bar with grid: no parenteral antibacterial injection and no foot trimming; White bar with cross hatches: parenteral antibacterial injection and foot trimming; Grey bar: no parenteral antibacterial injection and foot trimming.