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JOURNAL TITLE: Veterinary Record

PUBLISHER: BMJ Publishing Group

PUBLICATION DATE: 7 June 2019 (online)

DOI: 10.1136/vr.105378

**Prevalence of and risk factors for acute laminitis in horses treated with corticosteroids**

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Key words – Laminitis, corticosteroid, risk factor, prevalence

Word count - 2803

**Abstract**

A retrospective treated vs untreated study (study one) and multi-centre prospective cohort study (study two) were undertaken to determine the prevalence of, and risk factors associated with, acute laminitis in horses treated with corticosteroids. All horses ≥1 year old treated with corticosteroids January to December 2014 (study one) and January 2015 to February 2017 (study two) by two first opinion and referral hospitals in UK were included. Additionally, an untreated animal was identified for each treated animal (study one). Signalment, body condition (Study two only), previous relevant medical history, primary condition, corticosteroid therapy prescribed and occurrence of acute laminitis during or within 14 days of cessation of corticosteroid treatment were recorded. For study one, 205 cases and 205 controls were identified; two animals within each group (1%) developed laminitis. In total, 1565 animals were included in study two; laminitis period prevalence was 0.6% (95% CI 0.4-1.2%), with 10 cases in 1565 treated animals. There were significant associations between laminitis and breed (pony vs horse; p=0.01; univariable analysis only), the presence of a laminitis risk factor (history of laminitis or an underlying endocrinopathy; p<0.001; OR [95% CI] 18.23 [5.05-65.87]) and body condition (overweight/obese vs not; p=0.04; OR [95% CI] 4.0 [1.09-14.75]).

**Introduction**

Corticosteroids are used in clinical practice to treat a range of non-infectious inflammatory diseases affecting horses. Since their introduction to veterinary therapeutics over 40 years ago, they have been associated with a perceived increased risk of acute laminitis (Bailey and Elliott 2007; Cornelisse and Robinson 2004; Cornelisse and Robinson 2013). However, there is little scientific evidence to support this association in healthy animals (McGowan and others 2016) and direct causation has not been established (Bailey 2010).

There are several published case reports involving either single or small number of animals treated with corticosteroids that developed laminitis (Cohen and Carter 1992; Dutton 2007; Frederick and Kehl 2000; Lose 1980; Ryu and others 2004; Vandenabeele and others 2004; Winfield and others 2013). However, many of these animals had pre-existing laminitis risk factors. Indeed, a study of electronic medical records identified corticosteroid use (prednisolone only) as a risk factor associated with subsequent, but not initial, laminitis episodes (Welsh and others 2017). There have been five case control studies published. One prospective study evaluated the treatment of severe equine asthma with dexamethasone and 2/25 (8%) animals developed laminitis (Muylle and Oyaert 1973). In two retrospective case control studies of laminitis, 3/108 (3%) cases had a history of prior treatment with corticosteroids in the first study (Slater and others 1995) and no association with recent corticosteroid use was identified in the second study (Wylie and others 2013b). A retrospective case-control study of animals treated with prednisolone revealed that prednisolone therapy was not associated with an increase in laminitis incidence (Jordan and others 2017). Finally, a prospective case-control study of pasture and endocrinopathy-associated laminitis (PEAL) revealed a 5.7-fold greater odds of PEAL among horses that had

received corticosteroids within the 30 days prior to examination relative to control (healthy and lameness combined) horses that had not (Coleman and others 2018). However, prior corticosteroid use did not remain in the final multivariable model comparing PEAL cases to lameness controls alone or to healthy controls alone, suggesting that the association could have been confounded by another variable (Coleman and others 2018). More importantly, corticosteroid administration was uncommon in all groups of horses (Coleman and others 2018).

Other relevant studies include two retrospective reviews of laminitis in which 4/216 (1.9%) cases (Cripps and Eustace 1999) and 8/525 (1.5%) cases (Hood and others 1993) of laminitis were associated with corticosteroid therapy. In addition, in three retrospective reviews of cases treated with triamcinolone, 3/2000 (0.15%) (Bathe 2007), 1/205 (0.5%) (McCluskey and Kavenagh 2004) and 20/27898 (0.07%) (Hammersley and others 2015) animals treated with triamcinolone developed laminitis. In this last study, the risk of developing laminitis was significantly higher in the control population (Hammersley and others 2015). Adverse drug reaction reports from USA recorded only 19 cases of laminitis associated with corticosteroid therapy between 1987 and 2013 (i.e. 30 years; (USDA-NAHMS 2000). Finally, there have been several publications documenting high doses or long courses of corticosteroid treatment with no subsequent laminitis development (French and others 2000; Lepage and others 1993; Tumas and others 1994).

The aims of this study were to determine the prevalence of, and the risk factors associated with, acute laminitis in a population of adult horses treated with corticosteroids.

**Materials and Methods**

The study was approved by the Royal Veterinary College Clinical Research Ethical Review Board (URN 2014 1309).

*Study one: Retrospective treated vs untreated study*

The clinical database of the Royal Veterinary College equine hospital and first opinion practice were searched to identify all horses ≥1 year old that had been treated with corticosteroids between 1st January 2014 and 31st December 2014. Untreated animals were identified as an animal seen on the same day and by the same veterinarian as a treated animal. A random number generator was used to select the untreated animal if more than one suitable animal existed. Exclusion criteria included corticosteroid treatment or laminitis in the preceding 28 days and euthanasia or death in the first 14 days post corticosteroid treatment not attributable to laminitis. For all animals, the age, breed, sex, previous relevant medical history and whether the horse developed laminitis in the 14-day period immediately after treatment were recorded. The type, route, dose and duration of corticosteroid was recorded for treated animals.

*Study two: Multi-centre prospective cohort study*

All horses ≥1 year old treated with corticosteroids between January 2015 and February 2017 by Royal Veterinary College and Bell Equine first opinion equine practices and referral hospitals were included in a prospective cohort study. Exclusion criteria included corticosteroid treatment or laminitis in the preceding 28 days and euthanasia or death in the first 14 days post corticosteroid treatment not attributable to laminitis. The age, breed, sex, subjective assessment of body condition (underweight, ideal, overweight or obese), previous

relevant medical history, current medical problem being treated, corticosteroid therapy prescribed (type, route, dose and duration) and the occurrence of acute laminitis during or within the first 14 days following the cessation of corticosteroid treatment were recorded by the treating veterinarian using a standard recording form (supplementary information 1).

A sample size calculation assuming 80% power and 95% confidence, based on a previous study in which the prevalence of laminitis was 4% (Menzies-Gow and others 2017) indicated that 1060 animals were required. The sample size calculation was subsequently re-calculated, as the period prevalence of corticosteroid-associated laminitis after one year of data collection was 0.7%; this indicated that 1553 animals were required for study two.

**Data analysis**

Statistical analyses were performed using commercial statistical software (IBM SPSS Statistics Version 23 and Graphpad Prism Version 7). Continuous data was tested for normality using the Shapiro-Wilk test..

*Study one: Retrospective treated vs untreated study*

The treated and untreated groups were compared using an unpaired student t-test (age) and Chi-squared tests (breed and sex). Significance was accepted at $p \leq 0.05$. No further comparisons were appropriate as an identical number of animals within each group developed laminitis.

*Study two: Multi-centre prospective cohort study*

Laminitis period prevalence was calculated as the proportion of the population that developed laminitis during or within 14 days following cessation of corticosteroid treatment, over the 25-month period of data collection. Individual factors significantly associated with laminitis development (age, breed [pony or horse], sex, veterinary practice [first opinion or referral], presence of a laminitis risk factor [previous laminitis or an underlying endocrine disease], body condition [underweight, ideal, overweight or obese], corticosteroid preparation [active ingredient], route of administration [systemic, intrasynovial, local infiltration or inhaled], dose, duration or condition requiring treatment) were initially determined using univariable analysis. Significance was accepted at $p \leq 0.1$. Multivariable binary logistic regression with backwards-stepwise selection was then performed in order to determine the likelihood of these individual significant factors being associated with the development of laminitis, with only variables with $p \leq 0.05$ being retained in the final model. Interactions between risk factors were also tested. Interactions between risk factors were tested by calculating A*B for significant risk factors and entering A*B into the multivariable model. If the P value for the interaction term A*B was >0.05, there was no significant interaction between risk factors A and B and they were sequentially removed until all the risk factors had P values of ≤0.05 in the final model. The odds ratio (OR) and 95% confidence intervals were calculated for significant variables.

**Results**

*Study one: Retrospective treated vs untreated study*

In total, 205 treated and 205 untreated animals were included in the study. The treated animals were significantly (p=0.02) older (median 13 [interquartile range, 9 - 17] years) than the untreated animals (11 [6.75 – 17] years). The untreated group comprised a significantly

(p=0.03) greater proportion of mares (45%) compared to the treated group (33%). The breed distributions were similar between the two groups. Within the treated group, 42% were non-Thoroughbred horses, 28% were ponies, 16% were Thoroughbreds and 14% were of unknown breed. Within the untreated group, 41% were non-Thoroughbred horses, 34% were ponies, 19% were Thoroughbreds and 7% were of unknown breed.

The most common reasons for corticosteroid treatment were musculoskeletal problems and lameness (46%), followed by skin problems (22%) and respiratory problems (18%). Dexamethasone was the most frequently administered corticosteroid (51%), followed by triamcinolone acetonide (15%), methylprednisolone acetate (13%) and prednisolone (11%). Inhaled preparations were infrequently prescribed; beclamethasone (6%) and fluticasone (1%). The duration of therapy varied from a single administration to 4 weeks. All animals received doses that were within the recommended ranges for horses.

Two animals (2/205; 1%) within each group developed laminitis. The laminitis could not be attributed to sepsis/systemic inflammation or supporting limb lameness in any animal. Out of the two treated animals that developed laminitis, one was treated with dexamethasone and one was treated with both dexamethasone and prednisolone, and neither had any relevant previous medical conditions. Both untreated animals had a history of previously laminitis and one also had equine metabolic syndrome (EMS).

*Study two: Multi-centre prospective cohort study*

In total, 1565 animals were included in the study, of which 36.9% were mares, 60.8% geldings and 2.3% stallions, aged (median [interquartile range]) 11 (7-16) years. Of these, 55.8% were

non-thoroughbred horses, 25.9% Thoroughbreds, and 18.3% ponies. Subjective assessment of body condition considered 7.4% as underweight, 70.1% as ideal body condition, 20.3% as overweight and 2.2% as obese. In addition, 10.1% of animals had a laminitis risk factor present, namely a history of previous laminitis or an endocrine disease (equine metabolic syndrome or pituitary pars intermedia dysfunction [PPID]). Finally, 693 (44%) were treated by an equine referral hospital and 872 (56%) by a first opinion equine practice.

In total, 45.6% of animals were treated for orthopaedic disease and 54.4% were treated for other medical conditions. Furthermore, 50.5% of animals received the corticosteroids systemically, 34.5% via the intra-synovial route, 10.7% via local infiltration and only 4.3% via inhalation. Dexamethasone was the most frequently administered corticosteroid (41.0%), followed by triamcinolone acetonide (28.0%), methylprednisolone acetate (16.7%) and prednisolone (10.1%). Inhaled preparations were infrequently prescribed; beclamethasone (3.6%) and fluticasone (0.6%). The duration of therapy varied from a single administration to daily therapy for 3 months. All animals received doses that were within the recommended ranges for horses.

The period prevalence of laminitis was 0.6% (95% CI 0.4-1.2%), with 10/1565 animals treated with corticosteroids developing laminitis. The laminitis could not be attributed to sepsis/systemic inflammation or supporting limb lameness in any animal. Of these ten animals, three (30.0%) were treated for orthopaedic disease and seven were treated for other medical conditions; seven received systemic therapy (4 dexamethasone plus prednisolone, three only prednisolone) with the remaining three receiving intra-synovial medication (2 triamcinolone acetonide and 1 methylprednisolone); seven were euthanased, of which this

was due to laminitis severity or failure of the laminitis to respond to conservative treatment in four animals and due to deterioration of the primary disease in three animals.

Univariable analysis revealed significant associations between laminitis development and breed (horse vs pony; p=0.01), body condition (overweight/obese vs not; p=0.03) and the presence of a pre-existing laminitis risk factor (history of laminitis or an underlying endocrinopathy vs not; p<0.001). There was no significant association with age, practice, corticosteroid preparation, route of administration, dose, duration or condition requiring treatment. Multivariable analysis revealed significant associations between laminitis and the presence of a laminitis risk factor and an overweight/obese body condition (Table 1). Breed was not retained in the final model. In addition, there were significant interactions between three risk factors: between breed and body condition (p<0.001); between breed and presence of a laminitis risk factor (p<0.001); and between presence of a laminitis risk factor and body condition (p=0.003).

**Discussion**

The occurrence of laminitis in animals treated with corticosteroids was low in both studies (0.6-1.0%) and was similar to the frequency of veterinary-diagnosed laminitis reported in the GB general equine population of 0.5% (Wylie and others 2013a) and that in the untreated population in study one. Previously, a data mining study identified 0.07% of 27,898 triamcinolone-treated horses developed laminitis compared to 0.2% in the untreated control population (Hammersley and others 2015). Similarly, whilst 3.9% of animals treated with enteral prednisolone developed laminitis, this incidence rate was not different to that within the control untreated group (Jordan and others 2017). Thus, it would appear that laminitis

does not occur more frequently in populations of animals treated with corticosteroids than in the general equine population.

Univariable analysis revealed significant associations between the development of laminitis in animals treated with corticosteroids and breed (pony), body condition (overweight/obese) and the presence of a pre-existing laminitis risk factor (endocrine disease or a history of laminitis). Binary logistic regression analysis revealed that obese/overweight animals and animals with a pre-existing laminitis risk factor were four and eighteen times more likely to develop laminitis following corticosteroid treatment than animals without these, respectively. This was in agreement with an increased incidence of laminitis in animals with an endocrine disorder compared to those without within a group of animals treated with prednisolone (Jordan and others 2017). However, it should be remembered that breed (Welsh and others 2017), presence of an endocrinopathy, obesity (Coleman and others 2018) and previous laminitis (Wylie and others 2013b) are all risk factors for laminitis within the general equine population. In addition, it should be noted that the confidence intervals for these odds ratios were wide due to the small number of animals that developed laminitis.

Anecdotally, triamcinolone is perceived to be associated with a greater risk of laminitis in animals treated with corticosteroids compared to other steroid types (Cornelisse and Robinson 2013; McIlwraith 2010). However, no association between laminitis development and steroid type was apparent in this study. This is in agreement with a previous study in which there was no association between corticosteroid preparation and the first episode of laminitis; prednisolone prescription was associated with 5.3 times the hazard of subsequent laminitis episodes only (Welsh and others 2017).

There was no significant association between corticosteroid dose and laminitis development. However it should be acknowledged that the administered doses were all within the recommended dose ranges for horses. Future studies evaluating the effect of dose of the individual steroid types would require a more rigorous, controlled experimental study design using higher doses.

The development of laminitis during or within 14 days of the cessation of corticosteroid therapy was chosen as the outcome variable. This was based on previous publications which provided information regarding the time of onset of laminitis relative to corticosteroid administration. The occurrence of laminitis in animals treated with prednisolone was investigated and 75% developed laminitis either during or within 7 days of cessation of therapy (Jordan and others 2017); the remainder developed laminitis more than a month after cessation of therapy. Only one horse developed laminitis in association with triamcinolone therapy and this occurred one week after treatment (McCluskey and Kavenagh 2004). Seven out of eight individual case reports developed laminitis either during or within 14 days of cessation of therapy (Anon 2005; Frederick and Kehl 2000; Humber and others 1991; Lose 1980; Ryu and others 2004; Vandenabeele and others 2004; Winfield and others 2013). Additionally, the effects of triamcinolone on glucose metabolism in horses have been shown to persist for up to 8 days after administration (French and others 2000). If a horse developed laminitis after 14 days it was not included in the study as the time frame is too long to suggest a direct causal association (McGowan and others 2016).

The main limitation of this study was the lack of an untreated control population in study two. Whilst comparisons can be made with other studies with similar populations of horses and study one, ideally the study would have included a time-matched cohort of animals that was not treated with corticosteroids for a more appropriate comparison. In addition, cases of laminitis required a veterinary diagnosis. In first opinion practice, the condition often required initial identification by the owner or carer of the horse, to alert the attention of the treating veterinarian. It is possible that the laminitis may have gone unnoticed by the owner (Pollard and others 2017). Alternatively, owners may have chosen to deal with the laminitis themselves or involve a paraprofessional such as the farrier rather than the veterinarian (Potter and others 2017). Hence the prevalence in this study may be an underestimation of the true prevalence

It should be acknowledged that there may have been an inherent bias regarding case selection for corticosteroid treatment and variable recognition of pre-existing laminitis risk factors due to clinical judgment and variable experience of the treating veterinarian. The low frequency of ponies compared to horses treated with corticosteroids on both study one and study two may be a reflection of this due to the perceived concern that ponies are a phenotype that are at an increased risk of developing laminitis, especially if the animal is overweight or has an underlying endocrine disease.

This study investigated the development of laminitis in animals treated with corticosteroids. However, it should be acknowledged that many of the horses included in this study were probably also subject to management changes, including box rest and dietary changes related

to their primary condition that may have increased the risk of laminitis and were not accounted for.

In conclusion, the occurrence of laminitis in animals treated with corticosteroids in this study was low (0.6-1.0 %) and not dissimilar to previously published estimates of the frequency of veterinary-diagnosed laminitis in the GB horse and pony population (0.5%)(Wylie and others 2013a). There was a significant association between the development of laminitis in animals treated with corticosteroids and breed (pony), body condition (overweight/obese) and the presence of pre-existing laminitis risk factors. However, breed was not retained in the final multivariable model and these are also risk factors for laminitis within the general horse and pony population. Future research to determine whether screening animals for laminitis risk prior to corticosteroid therapy can guide case selection and reduce the overall risk of laminitis in clinical practice is required.

**Acknowledgements**

The authors would like to that the veterinarians at Bell Equine Hospital and the Royal Veterinary College equine practices and equine referral hospitals for their help with data collection.

Table 1: Analysis of the variables retained in the multivariable model for the development of acute laminitis in horses (n=1565) treated with corticosteroids

| **Variable** | **Odds Ratio** | **95% Confidence Interval** | **P value** |
|---|---|---|---|
| Body condition (overweight/obese vs not) | 4.0 | 1.09 – 14.8 | 0.04 |
| Presence of a laminitis risk factor (history of laminitis or an underlying endocrinopathy vs not) | 18.23 | 5.05 – 65.87 | <0.001 |

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