Intra-synovial triamcinolone treatment is not associated with incidence of acute laminitis

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Summary

Background: Intra-synovial corticosteroid injections are commonly used in the treatment of equine orthopaedic disease, but corticosteroid administration is widely considered a risk factor for the development of laminitis. Despite a list of putative mechanisms and a number of case reports of steroid-induced laminitis, no case-control or cohort studies investigating the association between use of intra-synovial corticosteroids and acute laminitis have been published.

Objectives: To quantify the risk of laminitis posed by intra-synovial triamcinolone acetonide (TA) administration in a mixed population of horses.

Study design: Retrospective observational cohort study.

Methods: Clinical records of horses registered with one large UK equine practice were reviewed retrospectively to identify all horses receiving intra-synovial TA treatment between 1 January 2007 and 31 December 2017. 1,510 horses were selected and records investigated for incidence of laminitis over a 4-month period following treatment. For each TA-treated horse, an untreated horse, individually matched by age, sex, date of treatment and client type, was selected from the clinical records. Untreated horses were then investigated for laminitis over the same 4-month period. Data was analysed in a 2×2 contingency table using Fisher's exact test.

Results: 489 horses were lost to follow-up and 55 horses were excluded, leaving 966 treated and matched, untreated horses. The incidence of laminitis over the 4-month study period in both groups was identical: 3/966 horses (0.31%) (95% C.I. [0.08%, 0.91%]), equivalent to 0.93 cases per 100 horses per year (P >0.9).

Main limitations: Retrospective study; large proportion (489/1510) of horses lost to follow-up; large proportion of study population were racehorses; selection method resulted in disproportionate selection of horses born before 2013; similar incidence between groups may reflect existing risk-based selection by clinicians.

Conclusions: Intra-synovial triamcinolone acetonide administration does not increase the risk of laminitis in this study population.

Introduction

Numerous case reports suggest that corticosteroid administration may be a risk factor for the development of laminitis. Causative mechanisms have been proposed and evidence for these has been reviewed [1-3]. However, a recent knowledge summary [4] found "no conclusive evidence to support a causal association between therapeutic systemic corticosteroid administration and the development of laminitis in healthy adult horses/ponies" and two recent studies found no association between corticosteroid use and laminitis [5,6].

Triamcinolone acetonide (TA) is a synthetic analogue of cortisol, the main naturally-occurring glucocorticoid, and is commonly used intra-synovially to treat equine orthopaedic disease [7,8]. Dosage varies according to target site, indication, and clinician preference. However, 18 mg has been cited as the maximum 'safe' dose [7,9]. Triamcinolone acetonide is a chemical derivative of triamcinolone. All subsequent references to triamcinolone mean triamcinolone acetonide. Studies looking specifically at triamcinolone [10–12] have reported a low incidence of laminitis in corticosteroid-treated horses. However, none included individually-matched controls.

Currently, clinical decision-making regarding intra-synovial corticosteroids is complicated by insufficient information on the risk of laminitis. The primary objective of this retrospective observational cohort study was to compare the incidence of laminitis in TA-treated horses with matched controls. The secondary objective was to quantify laminitis risk posed by triamcinolone acetonide.

Materials and Methods

Despite a number of studies investigating risk factors for laminitis [5,6,13,14], a recent review found inconsistent and often conflicting results [15]. Nonetheless, to minimise the effect of concurrent risk factors, the treated and untreated groups in the current study were matched according to age, sex, breed and season.

Since there is poor existing scientific evidence for a relationship between corticosteroids and laminitis, there is no evidence for an optimal time period for this study. However, a follow-up period of 4 months was used in order to maximise sensitivity for detecting iatrogenic laminitis whilst minimising the number of cases with 'naturally-occurring' (non-iatrogenic) laminitis.

Selection of treated cohort:

Clinical records of horses registered with one large UK equine practice were retrospectively reviewed to identify all horses receiving triamcinolone acetonide (Adcortyl[a]) between 1 January 2007 and 31 December 2017. In horses receiving multiple treatments, the date of first treatment was used. Cases referred from other practices were excluded due to lack of follow-up.

Selection of untreated cohort:

For each treated horse, untreated horses born in the same year, of the same sex (male or female), same client type, and seen by a veterinary surgeon during the same month as the treated horse, were identified, except that in some treated cases, sex and/or birth data were unavailable. When multiple horses matched these selection criteria, one horse was randomly selected (random number generation using Microsoft Excel). Sex and birth date were available for all selected, untreated horses. Untreated horses were included only once and were all available for follow-up for at least 4 months.

When no matched control was found, the search was repeated to identify untreated horses seen within 6 months of the treatment month. The method for this is outlined in Figure 1.

Power Calculation/Sample Size:

It was decided to include approximately 1,500 horses in each group. This would detect a difference in laminitis incidence of 0.5% and 1.6% with power of 83% at a significance level of 3% using a two-tailed Fisher's Exact test (G*Power 3.1.9.4). The study was powered for the primary outcome; no a priori power analysis was performed for analyses of secondary outcomes.

Following exclusion of cases, data from 966 treated and matched horses were analysed. A study of this size is able to detect a difference in incidence of 0.5% and 2.0% with power of 83% at a significance level of 2%.

Data Collection:

For all horses, the following data were recorded: Year of birth; Sex (male; female); Client type ('general equine'; 'equine trainer'; 'equine stud').

For treated horses, the following data were recorded: Treatment date; TA dose; Site of administration ('intra-articular/intra-synovial'; 'interspinous ligaments'; 'sacroiliac joint'; 'other').

Outcome Measures:

Patient records were searched for occurrence of laminitis up to 4 months after treatment. Presence of laminitis was defined as a horse examined by a veterinary surgeon, with a clinical note confirming diagnosis of laminitis.

Records containing the word 'laminitis' were reviewed by one experienced clinician, blinded to patient identity and treatment group, to answer the following question: 'on the balance of probabilities, do you believe the horse was suffering from laminitis?'

For horses deemed to have developed laminitis, the following data were collected: Date of onset of laminitis; Outcome following laminitis (recovery; death; loss to follow-up; continuation of disease).

Additionally, the clinical records were reviewed for any previous reference to either laminitis or endocrinopathy.

Each individual case was also followed up by phone to ask for further details regarding each horse's outcome following laminitis.

Horses presenting with laminitis at time of selection or that received TA treatment into non-intrasynovial sites were excluded. Treated horses that did not develop laminitis but were euthanased, deceased or lost to follow-up within 4 months after treatment were also excluded.

Data Analysis:

Fisher's exact test was used to compare the proportions of horses with laminitis in control and TA groups. The exact *P* value is reported. The odds ratio and relative risk for developing laminitis in the TA group were also calculated. Analyses of secondary outcomes on the association between laminitis and both sex and client type were performed with Fisher's Exact Test. In addition, the difference in age between laminitic and non-laminitic horses was assessed with Student's unpaired t-test. Data were analysed using GraphPad Prism (version 8.4.2) and 95% confidence intervals were calculated using the Wilson/Brown method for proportions, the Baptista-Pike method for odds ratios and the Koopman asymptotic score for relative risk. Data management was performed with Microsoft Excel.

Results

A database search in January 2018 identified a total of 4,100 TA treatment episodes (single or multi-joint) in 2,280 horses between 1 January 2007 and 31 December 2017. Patient records were sorted by database ID and the first 1,510 patient records selected. These records were evaluated from May 2018. 489 were lost to follow-up within the 4-month period. On detailed examination, 55 additional records were excluded: 31 received TA into a non-intrasynovial site (17 into interspinous ligaments; 5 into sacroiliac joints; 9 into other sites); 12 had no target site recorded; 9 had record errors (2 had incorrect date of birth; 7 had no record of TA treatment despite meeting the initial search criteria); 2 were general accounts not pertaining to individual horses; for 1 horse, no untreated control could be found. A flow chart to show recruitment of treated horses into the study is shown in Figure 2.

In total, 966 treated horses with individually-matched untreated controls were analysed. The distribution of 966 TA-treated horses across the year is shown in Figure 3 and reveals above average monthly treatments from March to September inclusive.

Population characteristics

Date of birth was available for 889 treated horses, although 678 were recorded as 1 January, introducing bias into age estimates. Of these 889 treated horses, median age at treatment was 4.0 years [IQR 3.0-8.4, range 0.9-27.7]. In the matched untreated horses, median age at selection was 4.1 years [IQR 3.0-8.6, range 0.3-27.8].

Sex was available for 907 treated horses and for all untreated horses. Of the 907 treated horses, 634 (69.9%) were male and 273 (30.1%) were female. Of the 966 untreated horses, 677 (70.1%) were male and 289 (29.9%) were female.

326 horses were reported as 'general equine' (33.8%), 602 as 'equine trainer' (62.3%), 7 as 'equine stud' (0.7%) and 31 as both 'equine trainer' and 'equine stud' (3.2%).

TA dose was reported for 207 treated horses (median total dose = 10 mg [IQR 10-16, range 3-21]). For the remaining 759 horses, the number of 10 mg ampoules billed on the treatment date was recorded (median ampoules = 1 [IQR 1-2, range, 0.5-5]).

Incidence of laminitis

The incidence of laminitis over the 4-month study period in both groups was identical: 3/966 horses (0.31%) (95% C.I. [0.08%, 0.91%]), equivalent to 0.93 cases per 100 horses per year (P >0.9). The odds ratio was therefore 1.0 (95% C.I. [0.23, 4.29]), as was the relative risk (95% C.I. [0.23, 4.32]). Of the six horses that developed laminitis, those treated were 8.8, 9.4 and 12.8 years old and the untreated horses were 5.7, 6.2 and 17.7 years old. All three treated horses were geldings and the untreated horses were two geldings and one mare. One untreated horse was recorded as 'equine trainer' and the remaining five were 'general equine'.

TA dose was reported for two treated horses that developed laminitis. One horse was administered 5 mg into both fore distal sesamoidean impar ligaments (total dose 10 mg); the other received 5 mg into a single metacarpophalangeal joint. The third horse had triamcinolone administered into the navicular bursa, but no dose was recorded (1 x 10 mg ampoule was billed). For treated horses that developed laminitis, laminitis occurred at 21, 51 and 55 days after treatment (mean 42 days). For untreated horses, the onset times were 10, 29 and 111 days after date of selection (mean 50 days). The six clinical cases of laminitis were observed on 12 May, 14 October and 4 November (TA-treated) and 26 March, 5 September and 28 November (matched horses).

Clinical records indicated no history of laminitis in the three treated horses that developed laminitis. One of the three untreated horses that developed laminitis had a previous history of the disease. Two of the 6 laminitic horses

were tested for endocrine disease after developing laminitis. One, a TA-treated horse (8-year-old Connemara gelding), was found to have mild insulin dysregulation 4 weeks after the laminitis diagnosis. The other, an untreated horse (17-year-old Thoroughbred gelding), was diagnosed with Pituitary Pars Intermedia Dysfunction (PPID) 6 months after developing laminitis.

Outcome was recorded for all 6 laminitic horses. Of the 3 treated horses, one developed chronic laminitis (subsequently lost to follow-up after 8 months), one was euthanased 16 months later due to chronic forelimb lameness unrelated to laminitis, and one recovered and was sold one year after developing laminitis. Of the 3 untreated horses, clinical signs resolved in two cases, and recurred in the third horse, which was eventually euthanased due to severe laminitis (owner-reported, unknown time frame).

Finally, data was collected to evaluate the relationships between laminitis and age, sex and client type. Among those horses with birth data (n = 1,855), the age (mean ± SD) of the laminitic horses was 10.0 ± 4.5 years (n = 6) and of non-laminitic horses was 6.3 ± 4.8 years (n = 1,849) (P = 0.06, two-tailed unpaired t-test). Among those horses with sex data (n = 1,873), 83% of the horses with laminitis (5/6) and 70% of those without laminitis (1,306/1,867) were male (P = 0.7, Fisher's Exact Test). Among all 1,932 animals, 83% of the horses with laminitis (5/6) and 34% of those without laminitis (647/1,926) were from a general equine client (P = 0.02, Fisher's Exact Test).

Discussion

In this study, there was no increase in risk of laminitis following administration of intra-synovial triamcinolone. This result is consistent with previous studies by Hammersley *et al*. [11], Jordan *et al*. [5], McGowan *et al*. [4], and Potter *et al*. [6], all of which found no increase in risk of laminitis following administration of corticosteroids.

The 4-month incidence of 0.31% of laminitis is comparable to previous reports of triamcinolone-treated horses (Table 1). The low incidence of 0.5% reported by McCluskey and Kavenagh [12] is notable given the higher doses of triamcinolone administered (50.7% of horses received 40 mg, and 48.8% received 80 mg triamcinolone per treatment). However, it is difficult to make a direct comparison as the follow-up period is not clearly reported in this study. For example, at least one horse "developed laminitis 18 months after TMC therapy". The incidence of laminitis reported in the current study is also similar to that reported in another recent study looking at various corticosteroid preparations [6]. Interestingly, the latter found no association between incidence of laminitis and type of corticosteroid prescribed, challenging the suggestion that triamcinolone, as a more potent agent than

prednisolone, may be associated with a higher risk of laminitis [4,12]. A retrospective cohort study by Jordan *et al*. [5] found a notably higher incidence of acute laminitis than this and other studies both in untreated controls (5.7%) and following oral prednisolone (3.8%). However, this may be due to the longer follow-up period with some cases of laminitis occurring many years after date of initial treatment. The incidence of laminitis in the general (untreated) equine population reported here also is similar to those previously reported (Table 1), with the notable exception of Jordan *et al*. [5].

Concurrent risk factors

Whilst there is little evidence of association between corticosteroid use and laminitis in healthy horses, the risk may be greater in horses that have endocrine disease, or are overweight/obese [4,5,6]. Furthermore, breed [5,6] and age [5] have both been identified as risk factors for laminitis in corticosteroid-treated horses, with higher risk in older horses and ponies/native breeds. However, these are all risk factors for naturally-occurring laminitis in the general equine population [13,15,20] and our study offers no evidence for any additional risk associated with corticosteroid use in these cases.

Unfortunately, the data in this study are insufficient to evaluate any seasonality in the occurrence of laminitis. Similarly, since prevalence of endocrinopathic disease and weight/body condition were not recorded for the entire study sample, our data can offer no indication as to whether these represent predisposing risk factors.

Notwithstanding the weak evidence shown here, age may be an independent risk factor for laminitis [5,13,15], or reflect the increased prevalence in older horses of PPID, which itself is a risk factor for laminitis [13,14]. The effect of client type on laminitis risk may reflect different management practices between the categories, lower prevalence of risk factors such as endocrine disease and obesity in Thoroughbred racehorses, or even different inherent breed-associated risk. Age may also underlie different incidences of laminitis between client type groups; mean age of treated horses in the 'general equine' group was 12.0 years, whereas the mean age of treated horses across the other groups was 4.0 years.

Limitations

As with many retrospective studies, some data were unavailable due to incomplete or sparse clinical records and a large proportion of treated horses (489/1510 [32.4%]) were lost to follow-up within 4 months of treatment. A convenience sampling method was used to select treated horses and this resulted in a disproportionate selection of horses born before 2013. Additionally, some horses were matched with untreated horses that were seen up to 6

months before or after date of treatment, resulting in variation in date of selection of treated and matched untreated horses.

It should be noted that there was no a priori power analysis to determine a sample size for the secondary analyses on age, sex and client type. Indeed, the incidence of laminitis was very low, limiting the value of these results. In particular, the *P* values should be interpreted with caution and with these limitations in mind.

This study population was biased towards Thoroughbred racehorses, with 640/966 horses (66.3%) belonging to the client groups 'equine trainer' and/or 'equine stud' and this may explain the lower incidence of laminitis in the current study than has been previously documented (Table 1).

The low incidence of laminitis may also reflect existing risk-based case selection, whereby clinicians are less likely to prescribe corticosteroids to horses they deem to be at greater inherent risk of laminitis (for example, if the horse has been diagnosed with PPID or EMS, is of a susceptible breed, or has previously been diagnosed with laminitis). Furthermore, there may be a diagnostic bias, with clinicians less likely to diagnose laminitis in animals they perceive to be at lower inherent risk, with other conditions such as solar bruising being diagnosed instead.

Conclusion

In conclusion, our data indicate no increased risk of laminitis associated with administration of intra-synovial triamcinolone acetonide. Whilst appropriate risk-based case selection remains a necessary mainstay of clinical case management, care must be taken not to overstate a link between corticosteroids and laminitis in the face of growing evidence to the contrary. Using the best available evidence, veterinarians must always balance both risks and benefits, and seriously consider the implications of withholding corticosteroids in cases where they represent the best therapeutic option.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

Research ethics committee oversight not required by this journal: retrospective study of clinical records.

Owner informed consent

Explicit owner informed consent for inclusion of animals in this study was not stated.

Data accessibility statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authorship

All authors were involved in the design of the study, and in the preparation of the manuscript. C. J. Haseler performed the data collection and C. J. Haseler and G. E. Jarvis jointly performed the data analysis. All authors have approved the final version of the manuscript.

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Figure legends

Fig 1: Protocol for selection of matched untreated horse where no suitable horse is available during treatment month.

Fig 2: Flow chart to show recruitment of treated horses into the study.

Fig 3: Distribution of treatment date by month (all 966 TA-treated horses).

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6. Tables

Study	Study type	Follow-up period	Incidence in treated population (%)	Incidence in general (untreated) population (%)
Current study	**Retrospective cohort**	**4 months**	**0.31% (n=3/966)**	**0.31% (n=3/966)**
Bathe [10]	Retrospective review of clinical records	Not specified	0.15% (n=3/2000)	N/A
McCluskey and Kavenagh [12]	Retrospective review of clinical records	Not specified	0.5% (n=1/205)	N/A
Hammersley *et al.* [11]	Retrospective cohort	90 days	0.07% (n=20/27898)	0.2% (n=134/56695)
Jordan *et al.* [5]	Retrospective cohort (time-matched)	Variable	3.8% (n=16/416)	5.7% (n=46/814)
Potter *et al.* [6]	Retrospective cohort (time-matched)*	14 days	1.0% (n=2/205)	1.0% (n=2/205)
Menzies-Gow *et al.* [17]	Retrospective review of clinical records	1 year	N/A	7.9-17.1%
Dorn *et al.* [18]	Retrospective study	6.5 years	N/A	1.5% (n=52/3582)
Buckley *et al.* [19]	Prospective longitudinal study	1 year	N/A	23.8% (n=20/84)

Table 1: Reported estimates of the incidence of laminitis in corticosteroid-treated and non-treated horses.

*Potter *et al*. [6] also included a second prospective cohort study, the details of which are not included in this table.