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CRITICALLY APPRAISED TOPIC

Systematic review of the association between intrasynovial corticosteroid use and laminitis—What is the evidence?

Paula Keiko Anadão Tokawa[1] | Raquel Yvonne Arantes Baccarin[1] | Gustavo Zanotto[2]

[1]Department of Internal Medicine, School of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo, Brazil

[2]Large Animal Clinical Sciences Department, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas, USA

Correspondence
Gustavo Zanotto
Email: gzanotto@cvm.tamu.edu

Summary

Anecdotal information has linked the clinical administration of intrasynovial corticosteroids with the development of laminitis in horses. This systematic review aims to compile and evaluate the level of current evidence from published works investigating this issue. A systematic search in PubMed, CAB Direct and Web of Science databases was conducted in February 2022. Studies were included if designed as experimental in vivo in horses, case series, observational cohorts (retrospective or prospective—with/without control group) or randomised clinical trials. A total of 237 studies were generated from the systematic search and after applying inclusion criteria, four were selected: two were designed as retrospective cohort studies, one included a retrospective and a prospective investigation, and the last one was a case series. Studies usually had a high risk of bias, and some also presented weaknesses such as a lack of controls or insufficient information (corticosteroid dose and treatment/follow-up period). Reported incidence of laminitis following corticosteroid intrasynovial application was low, similar to controls, when these were included. The small number of articles that fitted the inclusion criteria of this systematic review highlights the lack of high-quality evidence to draw conclusions. Current scientific information, mainly at a high risk of bias, suggests that there is no association between intrasynovial corticosteroid injection and laminitis in horses without concurrent risk factors.

KEYWORDS

horse, articular, corticosteroids, evidence, laminitis

INTRODUCTION

Intrasynovial corticosteroid therapy is commonly used in the treatment of joint disease in horses. Anecdotal evidence has linked its application with the development of laminitis in some cases (Rendle, 2019).

This systematic review aims to gather and evaluate the level of published evidence regarding the incidence of laminitis following intrasynovial corticosteroids use.

MATERIALS AND METHODS

A systematic search on PubMed, CAB Direct (CAB) and Web of Science (WoS) databases was conducted in February 2022. Terms included in each search strategy are described in Table 1.

Articles were selected if they had the full text available, were published in English and described the effects of intrasynovial use of corticosteroids and their relationship with the development of laminitis. Corticosteroids included were methylprednisolone acetate (MPA), betamethasone, triamcinolone acetonide (TA), dexamethasone (DEX) and isoflupredone. Articles including several different routes of administration for corticosteroids were selected if they specified the use of intrasynovial injections and provided the relevant information.

Study designs included were in vivo experimental studies with horses, case series, retrospective or prospective observational (cohort) studies (with or without a control group) and randomised clinical trials. Other study designs not mentioned above were not included. Articles were excluded if they were not relevant to the question of this review; investigated only the systemic use of

corticosteroids and their effects on laminitis development; or did not employ the corticosteroids described above.

GZ and PKAT were responsible for the creation of the search strategies and screened all titles and the preferred abstracts/articles, applying inclusion/exclusion criteria for the selection of the pieces. If any disagreement arose, RYAB was consulted and after arguments were presented, a discussion was followed, and a final decision was made.

All included articles were assessed through the methodological index for non-randomised studies (MINORS) tool for risk of bias classification (Slim et al., 2003). For each topic of this tool, a score was attributed (2 = reported and appropriate; 1 = reported and unappropriated; 0 = not reported/unclear) and a sum of all topics was made. For non-comparative studies, final scores of 13–16 were considered of low risk of bias and scores of 12 or less, classified as high risk of bias. Comparative studies were classified as low risk of bias if scores were 19–24, while high risk of bias was defined for studies with of scores 18 or less (Ajrawat et al., 2019; Slim et al., 2003).

RESULTS

Two-hundred and thirty-seven articles were identified from the systematic search conducted in the three databases. After screening of titles, 75 articles were selected. Removal of duplicates was performed followed by the access of abstracts. After application of inclusion/exclusion criteria, seven articles were fully accessed for further examination. Three of these were excluded as they were observing the effects of systemic corticosteroid therapy only. Finally, four articles met the selection criteria for inclusion in this systematic review.

All of the included papers were observational studies. A retrospective observational (cohort) design was employed in two articles (Haseler et al., 2020; Welsh et al., 2016), and Potter et al. (2019) performed one study as a retrospective cohort and one as a prospective investigation. One article was designed as a case series (McCluskey & Kavenagh, 2004).

After applying the MINORs tool, three studies were classified as high risk of bias (McCluskey & Kavenagh, 2004; Potter et al., 2019; Welsh et al., 2016), while one was classified as low risk of bias (Haseler et al., 2020; Figure 1). This was mainly due to their retrospective design, unavailable or unclear information about possible concurrent risk factors of horses included in the studies or unclear description of the employed follow-up time or loss to follow-up. Bias from questionable accuracy of data due to the retrospective nature of studies, weakness due to lack of control groups (McCluskey & Kavenagh, 2004; Welsh et al., 2016; and study 2 of Potter et al., 2019) and lack of information about the dose of corticosteroids (Welsh et al., 2016) or follow-up time (McCluskey & Kavenagh, 2004; Welsh et al., 2016) were also identified.

Only one article investigated the relationship between the incidence of laminitis with corticosteroid therapy administered via the intrasynovial route alone (Haseler et al., 2020). The other three studies encompassed several different routes of the administration of the therapy but also provided enough information regarding intrasynovial routes to allow their inclusion (McCluskey & Kavenagh, 2004; Potter et al., 2019; Welsh et al., 2016). Data extracted from the articles regarding population, follow-up, employed corticosteroid and dose, the incidence of laminitis and concurrent risk factors are available in Table 2.

Included articles showed low incidence of laminitis following intrasynovial corticoid application. In a series of 205 cases treated with TA, McCluskey and Kavenagh (2004) reported an incidence

Clinical relevance

- Current scientific information, at high risk of bias, suggests intrasynovial corticosteroids are not associated with laminitis in horses without concurrent risk factors (metabolic or endocrine disease, obesity and history of laminitis). [Correction added on 23 Jan 2023 after first online publication: In the preceding sentence, changes have been made to the article content to improve clarity in this version.]
- No safe dose or corticosteroid type was identified in the literature.
- Further higher levels of evidence studies are needed.

TABLE 1 Search strategy employed in each database

Database	Search strategy
PubMed	("Glucocorticoids"[Mesh] OR "corticosteroids"[tw] OR "Glucocorticoids" [Pharmacological Action] OR "Prednisolone"[Mesh] OR "prednisolone"[tw] OR "methylprednisolone"[Mesh] OR "Methylprednisolone"[tw] OR "Triamcinolone"[Mesh] OR "triamcinolone"[tw] OR "Betamethasone"[Mesh] OR "betamethasone"[tw] OR "Dexamethasone"[Mesh] OR "dexamethasone"[tw]) AND ("horses"[mesh] OR "horses"[tw] OR "equine"[tw] OR "foal"[tw] OR "mare"[tw] OR "gelding"[tw] OR "stallion"[tw] OR "yearling"[tw]) AND ("laminitis" OR "Laminitis")
CAB	("Glucocorticoids" OR "corticosteroids" OR "Glucocorticoids" OR "Synthetic glucocorticoids" OR "Prednisolone" OR "prednisolone" OR "methylprednisolone" OR "Methylprednisolone" OR "Triamcinolone" OR "triamcinolone" OR "Betamethasone" OR "betamethasone" OR "Dexamethasone" OR "dexamethasone") AND ("horses" OR "Horses" OR "equine" OR "foal" OR "mare" OR "gelding" OR "stallion" OR "yearling") AND ("laminitis" OR "Laminitis")
WoS	("Glucocorticoids" OR "corticosteroids" OR "prednisolone" OR "methylprednisolone" OR "Methylprednisolone" OR "triamcinolone" OR "betamethasone" OR "dexamethasone") AND ("horses" OR "equine" OR "foal" OR "mare" OR "gelding" OR "stallion" OR "yearling") AND ("laminitis" OR "Laminitis")

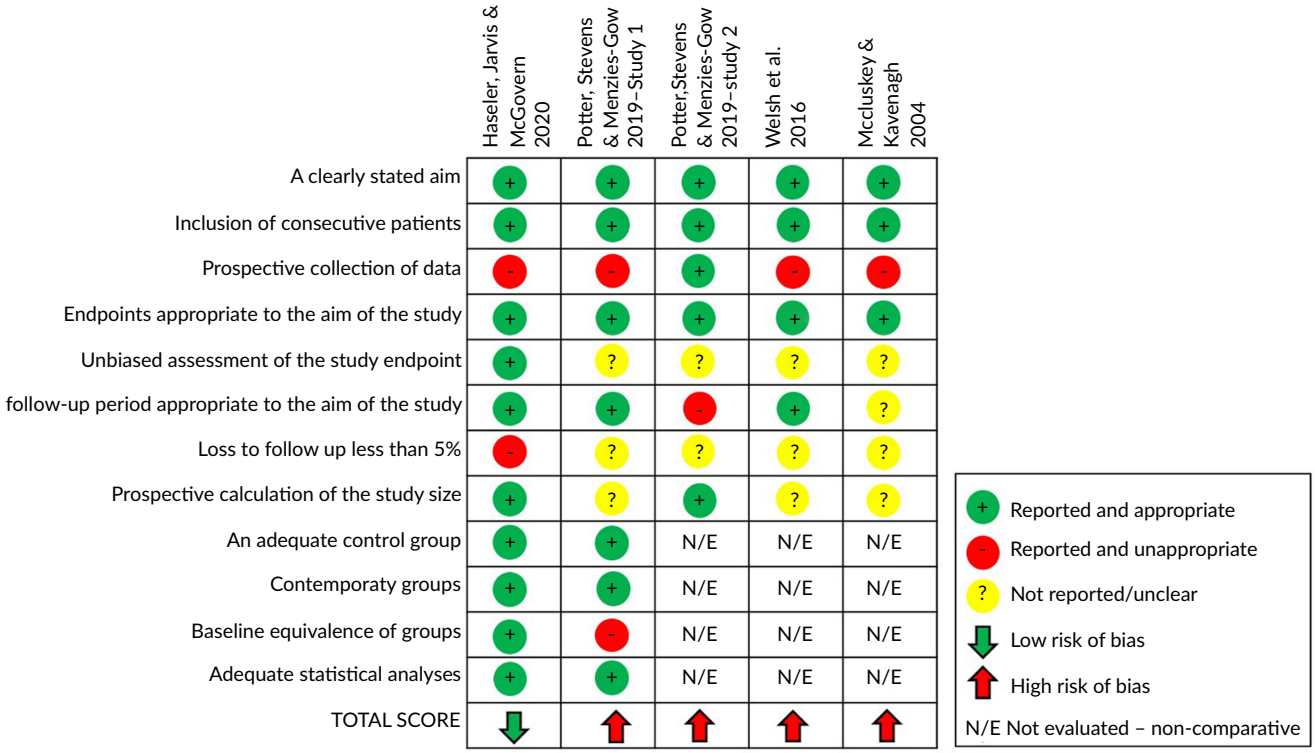

FIGURE 1 Risk of bias of included studies assessed through the methodological index for non-randomised studies tool. For each topic of this tool, a score was attributed (2 = reported and appropriate; 1 = reported and unappropriated; 0 = not reported/unclear) and a sum of all topics was made. For non-comparative studies, final scores of 13–16 were considered of low risk of bias and scores of 12 or less, classified as high risk of bias. Comparative studies were classified as low risk of bias if scores were 19–24, while high risk of bias was defined for studies with of scores 18 or less.

of laminitis of 0.5% (follow-up not clear)—which represented one case of a horse with history of laminitis (episode 7 months before the TA treatment). In the study of Welsh et al. (2016), electronic medical records (EMR) from seven different equine practices in the UK were evaluated and the authors reported that 3.1% of horses treated with TA, 3.6% treated with MPA, and 4.1% treated with DEX were identified with laminitis in the EMR—but routes of administration, time between corticosteroids application and laminitis development, corticosteroids' doses and concurrent risk factors were not described. Nevertheless, the authors did not find an association between the administration of any corticosteroids—at any route—with the first episode of laminitis (Welsh et al., 2016). Potter et al. (2019) reported a retrospective controlled and a prospective uncontrolled study with incidences of laminitis in 1% and 0.6%, respectively, of horses treated with corticosteroids. In their prospective study, the length of time between the corticosteroid application and the laminitis development was not clear, but in their retrospective study, a follow-up of 14 days after corticoid treatment was defined. In this study, controls presented same incidence of laminitis as treated horses. This was also a feature in the study of Haseler et al. (2020) where incidence of laminitis in the control and in the corticosteroid-treated groups was the same in a 4-month follow-up period (0.31% – 3/966). In this study, two horses in control group and one in the treated group had concurrent risk factors.

DISCUSSION

Intrasynovial corticosteroid therapy is commonly employed in the equine orthopaedic clinical practice (Cornelisse & Robinson, 2013). The concern of laminitis developing as a complication following corticosteroid therapy exists among veterinarians even though no mechanism has been proven to directly link exogenous intrasynovial corticosteroids with subsequent laminitis (Bailey, 2010; Knowles, 2018).

We have identified that there is very little quality data published regarding the incidence of laminitis in horses treated with intrasynovial corticosteroids. Overall, the reported incidence of laminitis following corticosteroid therapy in the included articles was usually low (0.31–1%). One study reported an incidence of laminitis of 3.1%–4.1% following administration of corticosteroids, usually employed by the intrasynovial routes (TA, MPA and DEX) (Welsh et al., 2016). However, the authors did not provide information about other risk factors that could have increased the risk of laminitis in horses included in this study. In the studies reporting lower incidences, the horses that developed laminitis usually had a history of previous episodes of laminitis or other medical conditions (such as endocrinopathies) suggesting that in healthy horses, free of risk factors, these numbers would be even lower, as suggested by other authors (McGowan et al., 2016).

The follow-up period in which laminitis was developed after the corticosteroid application should also be considered crucial, as

TABLE 2 Summary of included articles regarding population, follow-up, employed corticosteroid and dose, the incidence of laminitis and concurrent risk factors

Authors	Population	Follow-up	Corticosteroid	Dose	Incidence of laminitis	Risk factors present
Haseler et al. (2020)	CS group = 966 Control = 966 Total = 1,932	4 months	TA (intrasynovial route only)	10 mg (median)	CS treated and control same incidence 0.31% (3/966)	CS group 1/3 endocrinopathy Control group 1/3 previous laminitis episode 1/3 endocrinopathy
Potter et al. (2019)	1: CS group = 205 Control = 205 Total = 410 2: only treated horses *n* = 1,565	14 days	DEX, TA, MPA, PRED beclomethasone and fluticasone (1: several routes) (2: several routes, 34.5% intrasynovial)	within recommended ranges for horses	1: CS treated and control same incidence 1% (2/205). 2: 0.6% (10/1565), only 3/10 received intrasynovial CS.	1: CS group: no relevant previous medical condition Control group: both had previous laminitis episode and 1 also had EMS 2: Only specified the percentage of horses with risk factors in the total population – not known about the laminitic ones
Welsh et al. (2016)	Total cases analysed *n* = 70,481 of which CS treated *n* = 4,639	Followed up to first subsequent laminitis episode Or dead/lost to follow-up/ end of the study period	DEX, TA, PRED and MPA (several routes)	Not included in analysis (lack of information)	Incidence of laminitis in cases treated with different CS: DEX (4.1%), TA (3.1%), PRED (12.1%) and MPA (3.6%)	It was not specified if any of the horses that developed laminitis had any other risk factors
McCluskey and Kavenagh (2004)	*n* = 205 cases (132 horses)	not clear	TA (several routes—92.2% intrasynovial)	40–80 mg (only 1 horse treated with 10 mg)	0.5% (1/205)	Previous laminitis episode

Abbreviations: CS, corticosteroid; DEX, dexamethasone; MPA, methylprednisolone acetate; TA, triamcinolone, PRED, prednisolone acetonide; EMS, equine metabolic syndrome.

if too long has past, the laminitis development could mistakenly be attributed to the treatment. Despite this, the period for laminitis diagnosis after corticosteroid injection was not clear in many included articles. As for the ones including such information, great variation in the considered period was found (14 days to 4 months; Haseler et al., 2020; Potter et al., 2019).

The two articles that included control groups found a similar incidence of laminitis in both corticosteroid-treated and corticosteroid-untreated horses, suggesting that the development of laminitis in the treated group may have been unrelated to corticosteroid therapy (Haseler et al., 2020; Potter et al., 2019).

Doses of corticosteroids employed were reported in three articles, of which two used doses within the therapeutic range for horses while one employed higher doses (up to 80 mg of triamcinolone) per treatment (McCluskey & Kavenagh, 2004). Despite this difference, the incidence of laminitis in these articles was similarly low. It is important to highlight that included articles were mainly clinical studies which may reflect the usual caution employed by clinicians regarding certain characteristics presented by horses (e.g. obesity). In addition, no "safe" doses regarding avoidance of laminitis development were identified in the literature, so cautious use of corticosteroids is recommended in cases at risk (Cornelisse & Robinson, 2013). Dutton (2007) reported a legal case where a horse was injected with 80 mg of triamcinolone in each hock plus 20 mg of dexamethasone in the back. In court, it was concluded the case developed laminitis due to the corticosteroid overdose and the clinician was held responsible for the death of the horse. Despite the dosage being considered an important issue, one study did not provide information about the employed doses (Welsh et al., 2016).

Risk of bias in three out of the four articles included in this review was high. As most of them were retrospective studies, bias regarding the accuracy of records may arise (Haseler et al., 2020; McCluskey & Kavenagh, 2004; Welsh et al., 2016; and study 1 of Potter et al., 2019). In addition, some studies did not include a control group (McCluskey & Kavenagh, 2004; Welsh et al., 2016; and study 2 of Potter et al., 2019) and one of them was not able to include doses and period of corticosteroid use due to incompleteness of records (Welsh et al., 2016), information that could affect the results. Furthermore, two of the four articles included were not clear about the follow-up period of horses included in their studies.

Reviews reporting findings regarding incidence of laminitis following corticosteroid therapy, usually via systemic routes, have previously been published (Cornelisse & Robinson, 2013; Knowles, 2019; Rendle, 2019) although this is the first systematic review of literature relating to the subject. We found that, in the absence of any overt underlying metabolic or endocrine disease, obesity or history of laminitis, current scientific evidence does not support an association between intrasynovial corticosteroid injection and subsequent laminitis. Our findings also highlight the lack of high-quality evidence level regarding this topic, despite the controversy of opinions found among vets.

AUTHOR CONTRIBUTIONS

All authors have contributed to the study design, study execution, data analysis and interpretation, manuscript preparation and have reviewed and approved the final version.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICS STATEMENT

Systematic review of the literature. No ethical review or approval from local or national bodies was needed.

ORCID

Paula Keiko Anadão Tokawa https://orcid.org/0000-0002-9767-6423
Raquel Yvonne Arantes Baccarin https://orcid.org/0000-0001-9730-0840
Gustavo Zanotto https://orcid.org/0000-0001-8498-5246

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