A Comprehensive Systematic Review of Intra-Articular Corticosteroids: Symptom and Disease Modification Osteoarthritis Effects and the Potential Impact on Healthy Joints (Part 1)

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Abstract

Background: The importance of intra-articular corticosteroid treatment for osteoarthritis with its possible adverse effects requires a comprehensive review. Objectives: This review answers the following questions: 1) What evidence is available regarding the symptom-modifying and disease-modifying changes related to a single intra-articular corticosteroid injection for treating osteoarthritis? Moreover, 2) What evidence suggests corticosteroids are detrimental to equine joint health? Study design: Systematic review. Methods: A systematic search was conducted in June/2022 in PubMed, CAB, and the Web of Science. Inclusion criteria were applied to titles and abstracts. For each question, further criteria were applied. The risk of bias was assessed according to the study design. Results: We generated 6,417 titles, and 23 articles fit all inclusion criteria for single-injection corticosteroid treatments; 21 were included regarding corticosteroid effects on joint health. Studies were usually rated as having an unclear risk of bias. Single-injection protocols lead to short-term symptom-modifying osteoarthritic changes with conflicting results regarding disease-modifying osteoarthritis. Healthy joints demonstrated disturbances in metabolism and tissue changes, with dose-dependent effects found in vitro. Main limitations: There is a lack of studies regarding the topics–primarily for equine species. Conclusions: Symptom-modifying osteoarthritic changes after a single injection are short-term; however, a consistent disease-modifying osteoarthritis effect is yet to be established. Joint health appears to be disturbed by corticosteroids as their effects on normal joints show adverse changes in tissues and metabolism.

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SUMMARY

Background: The importance of intra-articular corticosteroid treatment for osteoarthritis with its possible adverse effects requires a comprehensive review.

Objectives: This review answers the following questions: 1) What evidence is available regarding the symptom-modifying and disease-modifying changes related to a single intra-articular corticosteroid injection

for treating osteoarthritis? Moreover, 2) What evidence suggests corticosteroids are detrimental to equine joint health?

Study design: Systematic review.

Methods: A systematic search was conducted in June/2022 in PubMed, CAB, and the Web of Science. Inclusion criteria were applied to titles and abstracts. For each question, further criteria were applied. The risk of bias was assessed according to the study design.

Results: We generated 6,417 titles, and 23 articles fit all inclusion criteria for single-injection corticosteroid treatments; 21 were included regarding corticosteroid effects on joint health. Studies were usually rated as having an unclear risk of bias. Single-injection protocols lead to short-term symptom-modifying osteoarthritic changes with conflicting results regarding disease-modifying osteoarthritis. Healthy joints demonstrated disturbances in metabolism and tissue changes, with dose-dependent effects found *in vitro* .

Main limitations: There is a lack of studies regarding the topics–primarily for equine species.

Conclusions: Symptom-modifying osteoarthritic changes after a single injection are short-term; however, a consistent disease-modifying osteoarthritis effect is yet to be established. Joint health appears to be disturbed by corticosteroids as their effects on normal joints show adverse changes in tissues and metabolism.

Keywords: horse, corticosteroids, osteoarthritis, single injection, normal joints

CLINICAL RELEVANCE

- The evidence on single intra-articular corticosteroid injections for the treatment of osteoarthritis and its effects on normal joints are scarce, primarily unclear, and characterized by a high risk of bias, especially considering only equine studies.
- A single injection of corticosteroids has limited symptom-modifying osteoarthritic changes with unclear disease-modifying osteoarthritis changes.
- When used in healthy joints, corticosteroids appear to have detrimental effects on articular metabolism.

INTRODUCTION

Intra-articular corticosteroids have been used to treat joint diseases since the early 1950s in humans (Hollander et al., 1951). A few years later, joints were treated with corticosteroids in horses as well (Wheat, 1955). The potent anti-inflammatory characteristics of corticosteroids leading to pain relief made these treatments popular; however, additional research revealed adverse effects on joint integrity (Goodrich & Nixon, 2006; McIlwraith, 2010). Despite being a highly controversial therapy for joint disease, corticosteroids were the intra-articular (IA) treatment of choice among equine practitioners in recent surveys (Goodrich & Nixon, 2006; Zanotto & Frisbie, 2021; Velloso Alvarez et al., 2020).

Given their substantial popularity in the face of controversy, this systematic review identified and appraised the evidence regarding corticosteroids as an IA therapy for horses. The authors intend to answer the following questions: 1) "What is the available evidence regarding the symptom-modifying and disease-modifying effects of a single IA injection of corticosteroid for treating osteoarthritis (OA)?"; and 2) "What is the current evidence suggesting that corticosteroids are detrimental to joint health?".

METHODS

This systematic review followed the PRISMA guidelines (Moher et al., 2009). Using three databases (PubMed, CAB Direct, and Web of Science), a systematic search was made of all published articles up to 20 July 2022, employing the terms described in Table 1.

Inclusion criteria were articles with a full text available, published in English, evaluating the effects of IA corticosteroid injections alone on limb/arm/leg joints. *In vitro* studies were only included when investigating equine tissues. Corticosteroids included methylprednisolone acetate (MPA); betamethasone (BTM), triamcinolone acetonide (TA), triamcinolone hexacetonide (TH); dexamethasone (DEX), and isoflupredone acetate

(IPA). Acceptable study designs were pre-clinical studies, randomized clinical trials (RCTs), prospective or retrospective cohorts, case-controls, crossovers, or pilots; Case reports, reviews, expert opinions, meeting abstracts, conference papers, and designs other than those cited previously were excluded. When equine species were the investigated population, at least a comparison from the baseline of the corticosteroid treatment effect was required. For other species, a negative control as the comparison group was required for inclusion. Other exclusion criteria included other joint types (e.g., temporomandibular), studies only containing groups with injections of corticosteroids plus other medications (e.g., local anesthetics, hyaluronic acid, or antibiotics), and patients with rheumatoid arthritis, juvenile idiopathic arthritis, hemarthrosis, or septic arthritis.

Additional criteria were added according to each question in this review. For question one, articles that investigated the effects of a single IA corticosteroid injection as treatment for OA in horses were included. Because veterinary science is often based on human practice, studies with humans as the investigated population were also included. No *in vitro* studies were considered for this question. For question two, we considered only studies investigating the effects of IA corticosteroid treatment in healthy joints in horses (*in vivo*) or exposure of corticosteroids to normal/healthy equine joint tissues (*in vitro*).

Risk of bias was assessed for RCTs using the Cochrane Risk of Bias tool, in which possible sources of bias are evaluated separately, and their risks are rated as "low," "unclear," or "high" (Higgins et al., 2011). According to the tool, an RCT is considered to have a final "low risk of bias" criteria only if all its items are classified as "low risk." If one or more items are classified as "unclear," the final criterion of the study is "unclear risk," and if at least one of them is classified as "high risk," the study is considered to have a "high risk" of bias. Studies for horses *in vivo* were assessed similarly. Observational studies (when included) were rated using the methodological index for non-randomized studies (MINORS) tool, which rates items as reported and appropriate (score = 2), reported and inappropriate (score = 1), or not reported (score = 0) (Slim et al., 2003). Scores were then summed and classified as low risk of bias (final score 13–16 for non-comparative studies or 19–24 for comparative studies) or high risk of bias (scores of [?] 12 for non-comparative studies or [?] 18 for comparative studies) (Ajrawat et al., 2019; Slim et al., 2003).

Primary outcomes of interest were symptom-modifying changes (lameness/patient-reported outcome measures [PROMs]) and disease-modifying changes (imaging, histology, biochemistry, and others).

RESULTS

The databases yielded 6,417 studies (3,213 in PubMed, 507 in CAB direct, and 2,697 in Web of Science), and one study was included from other sources. After removing duplicates through a reference manager software (Zotero(r)), the abstracts of 4,524 titles were screened independently by two authors. Disagreements were among all authors until resolution. We excluded 4,365 articles because they did not investigate corticosteroids applied through the IA route, or not alone, or investigated diseases other than OA, or were not published in English. We subjected 159 articles to full-text analysis. After applying the general inclusion criteria, 95 articles were selected for screening according to the criteria of each study question.

Twenty-three articles fit all inclusion criteria for question 1, and 21 were included for question 2 (Figure 1). Summaries of included studies for each question are available in supplementary material 1 and 2. Okike et al. (2021) included two investigations; however, only the case-control study was included in the results, as the retrospective cohort investigated the effects of corticosteroids plus local anesthetics. Some of the papers also investigated other therapies (e.g., hyaluronic acid [HA] or platelet-rich plasma [PRP]); however, comparison of these to corticosteroids is beyond the scope of this review, so only the corticosteroid and negative control groups of these studies were considered.

Question 1. What evidence is available regarding symptom-modifying and disease-modifying changes after a single IA injection to treat OA?

Twenty-three articles were included to answer question 1. Of these, 16 focused on humans (12 RCTs, one crossover, one case-control, one retrospective cohort, and one pilot) (Gaffney et al., 1995; Jones & Doherty,

1996; Young et al., 2001; Carette et al., 2003; Meenagh et al., 2004; Heyworth et al., 2008; Chao et al., 2010; Leung et al., 2011; Yavuz et al., 2012; Gialanella & Bertolinelli, 2013; Lattermann et al., 2017; Shrestha et al., 2018; Mendes et al., 2019; Okike et al., 2021; Latourte et al., 2022; Nunes-Tamashiro et al., 2022). Seven studies included horses as the study subjects (five pre-clinical*in vivo* and two RCTs) (Todhunter et al., 1998; Fubini et al., 2001; Kay et al., 2008; de Grauw et al., 2016; Ekstrand et al., 2019; Kearney et al., 2021; de Clifford et al., 2021). The risk of bias was considered unclear/high in most studies, with only four RCTs, one crossover, and one retrospective pilot study having a low risk of bias (Figure 3).

Lesions investigated in studies included (in humans) knee OA (ten studies), anterior cruciate ligament injury (one study), rapidly destructive hip disease (RDHD) (one study), shoulder adhesive capsulitis (one study), shoulder rotator cuff tendinopathy (one study), and OA of the carpometacarpal joint of the thumb (two studies). In horses, there was lipopolysaccharide-induced joint inflammation of the fetlock/carpus (five studies), naturally occurring middle carpal joint OA (one study), and lameness associated with joint pain (responsive to IA block) (one study). Human studies included 40 to 465 patients, with one study reporting the number of joints as the experimental unit (757 joints). This experimental unit was primarily employed in equine investigations in which sample numbers ranged from 11 to 41 joints. TA was the most investigated corticosteroid (ten studies; doses were 9–12 mg for horses and 40–80 mg for humans), followed by TH (five studies; doses of 5–40 mg for humans), MPA (five studies, 0.1 mg/kg for horses and 40–120 mg for humans), BTM (two studies; 3–6 mg for humans), and DEX (one study; 0.01–3 mg for horses). The specific corticosteroid type employed was not mentioned in two studies in which authors investigated the effects of IA corticosteroids in general. Follow-up varied from 48 hours to 6 weeks in equine studies and four weeks to five years in human investigations.

Symptom-modifying effects

Equine studies

Outcome measures regarding symptom-modifying changes were described in five equine studies (Kay et al., 2008; de Grauw et al., 2016; Ekstrand et al., 2019; Kearney et al., 2021; Clifford et al., 2021), and these included lameness, joint circumference, edema or effusion, range of motion (ROM), response to flexion test, skin temperature, and composite welfare score.

TA improved lameness by one or more grades in two studies with follow-ups of 11 days and three weeks (Kay et al., 2008; de Grauw et al., 2016). In another study, most horses treated with TA did not show improvement in lameness, with some even worsening at a 6-week follow-up (Clifford et al., 2021). Similarly, joint effusion showed improvements in a shorter-term study (three weeks) (de Grauw et al., 2016) with no significant changes for more extended periods (six weeks) (Clifford et al., 2021). Improvements in joint edema and ROM were reported following TA injection in one paper (11 days) (Kay et al., 2008) with no changes in joint circumference (Kay et al., 2008; Kearney et al., 2021) or composite welfare score (five weeks) (Kearney et al., 2021). Response to flexion was assessed by one study with a maximum of 6-week follow-up, and the authors reported no changes or worsening of response in most cases (Clifford et al., 2021).

DEX was assessed by one study, which demonstrated improved lameness (0.5–1 grade, 30-hour follow-up); however, the authors found no changes in joint circumference or skin temperature (74-hour follow-up) (Ekstrand et al., 2019). There were no studies reporting symptom-modifying osteoarthritic (SMOA) effects following a single IA injection of other corticosteroid types in horses.

Human studies

PROMs were the most studied outcome measure for symptom-modifying changes in humans, and more than one modality was usually applied (visual acuity scale, WOMAC, PGA, SF-36, SPADI, and others). Functional tests, ROM, joint tenderness or stiffness, and physician global assessment were also assessed in some studies.

TA consistently improved all PROMs in four studies, with only one author reporting no significant changes (Lattermann et al., 2017). Improvement time after TA injection varied from 4–12 weeks (Chao et al., 2010;

Yavuz et al., 2012; Gialanella & Bertolinelli, 2013; Shrestha et al., 2018). TA improved active ROM for up to 12 weeks, while no changes were found in passive ROM (Gialanella & Bertolinelli, 2013). Non-steroid use was not affected by TA injection when evaluated by one group (Gialanella & Bertolinelli, 2013).

When TH was assessed, significant improvements in at least one PROM in all five studies investigating this corticosteroid were found, although most reported improvements only up to 12 weeks (Gaffney et al., 1995; Carette et al., 2003; Meenagh et al., 2004; Mendes et al., 2019), with one author observing more extended positive effects (up to 52 weeks) (Nunes-Tamashiro et al., 2022). TH use did not affect functional tests and joint tenderness and stiffness (Mendes et al., 2019; Nunes-Tamashiro et al., 2022), (Meenagh et al., 2004). Effects on ROM were inconsistent; one study found significant improvements up to 24 weeks (Carette et al., 2003), while two others reported no significant changes (Mendes et al., 2019; Nunes-Tamashiro et al., 2022).

MPA was investigated in three studies with human patients, which demonstrated improvements in PROMs in all despite the duration of reported effects varying with one crossover demonstrating improvements up to three weeks only (Jones & Doherty, 1996); others showed improvements for up to 12 weeks (Young et al., 2001; Yavuz et al., 2012). No significant changes were found for functional tests after MPA treatment (Jones & Doherty, 1996; Young et al., 2001).

BTM was investigated in two studies, and again, conflicting results were found with no significant changes in PROMs, function tests, or ROM in 26 weeks reported by Heyworth et al. (2008) and significant improvements for PROMs and functional tests at 12 weeks in Yavuz et al. (2012). Finally, one author did not specify corticosteroid type but found significant improvements after corticosteroid injections in pain perception, functional tests, and analgesic use at 24 weeks (Leung et al., 2011).

Disease-modifying effects

Equine studies

Outcome measures regarding disease-modifying changes were less common but reported in four equine studies (Todhunter et al., 1998; Kay et al., 2008; Kearney et al., 2021) and included synovial fluid (SF) measurements (total protein [TP], cell counts, OA biomarkers, glycosaminoglycans, and prostaglandin E_2[PGE_2]), histopathology of cartilage and synovial membrane (SM), and measurements of protein synthesis and total proteoglycans in cartilage.

In equine studies, TA showed improvements by decreasing SF TP, reducing metalloproteinase (MMP) activity and chemokines (CCL2) (Kay et al., 2008; Kearney et al., 2021); however, drawbacks such as increased PGE_2 SF concentrations were also found, was a transient decrease in glycosaminoglycans (GAG) (Kearney et al., 2021). Results regarding white blood cell (WBC) counts in SF were not consistent between studies (Kay et al., 2008; Kearney et al., 2021).

MPA was evaluated in two equine studies, in which one found no significant changes regarding SF, TP, cell counts, histopathology of cartilage and SM, and proteoglycan (PG) and protein synthesis in cartilage. However, increases in small PG were found by one author (Todhunter et al., 1998), and suppression of matrix protein markers of chondrocyte differentiation was found by another, which could be associated with cartilage degeneration (Fubini et al., 2001).

Human studies

In human studies, TA showed improvements regarding SF concentration of OA biomarkers, with an elevated risk of worsening radiographic changes following injection (Lattermann et al., 2017; Okike et al., 2021).

Despite being a feature associated with TH, which showed worsening radiographic scores in 41% of patients included in Nunes-Tamashiro et al. (2022), these numbers were significantly higher in the control group (76%). No significant changes were found in ultrasonography regarding synovial hypertrophy after TH injection (Mendes et al., 2019).

MPA, assessed only by one paper, improved SM immunohistochemistry; however, no other disease-modifying osteoarthritis (DMOA) measures were evaluated (Young et al., 2001).

One study did not specify corticosteroid type but reported no significant changes regarding the risk of total knee arthroplasty or radiographic worsening after IA injection at the five-year follow-up (Latourte et al., 2022).

Corticosteroid type comparisons

Only one study compared corticosteroids (MPA, TA, and BTM) between themselves and placebo (Yavuz et al., 2012). All the corticosteroids showed significantly better results than placebo in PROMs and functional states, with MPA superior to TA and BTM up to three weeks and no significant differences among the three from three to 12 weeks.

Question 2. What is the evidence suggesting that corticosteroids are detrimental to normal joint health?

Twenty-one articles were included to answer question 2. These were 10 pre-clinical *in vivo* studies (Saari et al., 1992; Frisbie et al., 1997; Frisbie et al., 1998; Murray et al., 1998; Hills, Ethell & Hodgson, 1998; Todhunter et al., 1998; Robion et al., 2001; Céleste et al., 2005; Knych et al., 2017; Knych et al., 2018) and 11 *in vitro* investigations (Murphy et al., 2000; Fubini et al., 2001; Frean, Cambridge & Lees, 2002; Tung, Venta & Caron, 2002; Tung et al., 2002; Richardson & Dodge, 2003; Doyle et al., 2005; Byron et al., 2008; Busschers, Holt & Richardson, 2010; Palma et al., 2019a; Palma et al., 2019b). Risk of bias was rated for all *in vivo* studies, which were mainly considered as "unclear risk," with two rated as "high risk" (Figure 3). Summaries are available in Supplementary Material 2.

In vivo **studies**

In *in vivo* studies, seven authors investigated the effects of corticosteroids in normal joints alone (Saari et al., 1992; Murray et al., 1998; Hills, Ethell & Hodgson, 1998; Robion et al., 2001; Céleste et al., 2005; Knych et al., 2017; Knych et al., 2018), while three other included normal joints injected with corticosteroids as one of the groups (Frisbie et al., 1997; Frisbie et al., 1998; Todhunter et al., 1998). These studies considered only results of comparing negative control (normal joints + saline) from corticosteroid groups (injected in normal joints). MPA (60–100 mg or 0.1 mg/kg) was the most investigated corticosteroid (six studies), followed by TA (9–12 mg) (three studies) and IPA (8 mg) (one study), and follow-up time ranged from 36 hours to 91 days.

Symptom effects

In three studies (Murray et al., 1998; Robion et al., 2001; Céleste et al., 2005), the authors determined if corticosteroids injected in normal joints would cause any drawbacks, such as signs of lameness or joint effusion. No significant changes regarding these outcomes were found after injections of MPA or TA.

Effects on joint structure or metabolism

Effects changes on joint structure, or metabolism were investigated in all *in vivo* studies through outcomes such as analysis of SF content and volume, histology, histochemistry, and cartilage metabolism.

SF analysis was included in seven studies (Saari et al., 1992; Frisbie et al., 1997; Frisbie et al., 1998; Todhunter et al., 1998; Robion et al., 2001; Céleste et al., 2005; Knych et al., 2017). In three studies, MPA decreased SF volume in joints (Frisbie et al., 1998; Robion et al., 2001) with no or transient changes in WBC counts and total solid content (Saari et al., 1992; Todhunter et al., 1998; Robion et al., 2001); however, significant increases in TP were found by Frisbie et al. (1998). MPA injections also increased SF concentrations of GAG, PG, and HA in two studies (Saari et al., 1992; Frisbie et al., 1998).

When TA was evaluated, no significant changes were found in TP or WBC counts (Céleste et al., 2005; Knych et al., 2017), and no significant changes in color were found in two studies (Céleste et al., 2005; Knych et al., 2017). One study noted significantly higher scores (demonstrating more changes) in SF color

compared to controls (Frisbie et al., 1997). Mucin content was decreased, while GAG and HA concentrations were significantly increased in TA-treated joints (Frisbie et al., 1997).

Biomarker concentrations in SF after MPA and TA were also evaluated (Robion et al., 2001; Céleste et al., 2005). Both corticosteroids were found to increase aggrecan 846 and KS epitopes – suggesting an increase in PG release. CPII, on the other hand, was found to be decreased after the second MPA injection (suggesting inhibition of collagen synthesis), while increases were found after TA (Robion et al., 2001; Céleste et al., 2005). TA also increased concentrations of C1,2C –, which would reflect collagen degradation (Céleste et al., 2005).

Two studies evaluated Gene expression in SF for TA and IPA (Knych et al., 2017; Knych et al., 2018). MMP-1 and -9 were elevated up to 14 days and 96 h, respectively, while collagen genes were downregulated from 12 h to 42 days after TA IA injection (Knych et al., 2017). When IPA was evaluated, only a transient increase in MMPs followed by a persistent decrease (MMP-1 and -9) was found for up to 42 days with no significant changes in the expression of collagen genes (Knych et al., 2018).

Changes in cartilage and SM

Gross evaluation of cartilage was performed in three studies, which reported that TA or MPA injected in normal joints showed no changes in cartilage appearance (Frisbie et al., 1997; Murray et al., 1998; Frisbie et al., 1998).

Histologic examination of SM was performed in three studies (Frisbie et al., 1997; Frisbie et al., 1998; Todhunter et al., 1998). MPA promoted only mild to no significant changes in cellular infiltrate, proliferation of synovial cells, SM intimal hyperplasia, or fibrous tissues, having only effects on the decrease of SM vascularity (Frisbie et al., 1998; Todhunter et al., 1998). Regarding TA, a significant decrease in inflammatory cell infiltration and intimal cell hyperplasia was found, as was reduced SM subintimal fibrosis (Frisbie et al., 1997).

Histology of articular cartilage was also reported, and no significant changes were found after MPA-injected joints in one study (eight-day follow-up) (Todhunter et al., 1998), while the same corticosteroid worsened histologic scores of articular cartilages with longer follow-up (72 days) (Frisbie et al., 1998). TA effects on cartilage histology were investigated by only one group (Frisbie et al., 1997), which found a significant decrease in pathological changes associated with TA treatment.

Articular PG synthesis and GAG content in cartilage were evaluated. MPA significantly decreased PG and GAG synthesis in normal joints with increases in the synthesis of small proteoglycan monometers (Todhunter et al., 1998), while TA caused a significant increase in GAG synthesis (Frisbie et al., 1997). Total GAG content in cartilage after TA or MPA treatments was not significantly different from controls. However, TA or MPA-treated joints demonstrated a significant loss of SOFG staining in articular cartilage (Frisbie et al., 1997; Frisbie et al., 1998).

MPA injected in normal joints increased collagen and TP synthesis of joint tissues collected postmortem at eight days of follow-up (Todhunter et al., 1998).

Biomechanical properties of normal cartilage that received corticosteroid injections were assessed by Murray et al. (1998), who performed indentation testing postmortem and evaluated the material properties of the cartilage of joints receiving MPA. The authors found that MPA-treated joints were thinner, more compressible, and had less stiff cartilage than controls.

Diagnostic imaging changes

Radiographs were performed in three studies, 30- and 56-days, following IA injections of MPA or TA, and no significant changes were found (Frisbie et al., 1997; Frisbie et al., 1998; Robion et al., 2001).

In vitro **studies**

In *in vitro* studies, four authors investigated effects of corticosteroids in normal cartilage/tissues (without inflammatory stimulus) (Doyle et al., 2005; Byron et al., 2008; Palma et al., 2019a; Palma et al., 2019b) and seven studies included normal tissues exposed to corticosteroids as one of the control groups and reported their results (Murphy et al., 2000; Fubini et al., 2001; Frean, Cambridge & Lees, 2002; Tung, Venta & Caron, 2002; Tung et al., 2002; Richardson & Dodge, 2003; Busschers, Holt & Richardson, 2010). The corticosteroids were MPA/MPS (four studies), TA (four studies), DEX (four studies), and BTM (one study). Concentrations ranged from 0.001 to 10 mg/mL or 10^2 to 10^{10} for MPA, 0.06 mg/mL or 10^{-10} M to 10^{-4} M for TA, 10^{-10} M to 10^{-4} M for DEX, and 0.1 to 100 ?g/mL for BTM. Nine studies were performed with equine chondrocytes (Fubini et al., 2001; Tung et al., 2002; Tung, Venta & Caron, 2002; Richardson & Dodge, 2003; Doyle et al., 2005; Byron et al., 2008; Busschers, Holt & Richardson, 2010; Palma et al., 2019a; Palma et al., 2019b), one with equine cartilage explants (Murphy et al., 2000) and one with experiments in both (Frean, Cambridge & Lees, 2002). Follow-ups ranged from 6 hours to 13 days. Outcome measurements included PG and collagen synthesis, PG degradation, total PG and GAG, GAG content in cartilage, total GAG content in media, total cartilage DNA content, oxidative profile, gene expression proteolytic enzymes, extracellular matrix (ECM) components, and inflammatory proteins.

Cartilage metabolism

Four studies investigated changes in PG synthesis after the application of corticosteroids. MPA decreased PG synthesis in a dose-dependent way (Murphy et al., 2000; Doyle et al., 2005; Byron et al., 2008); however, one group reported that it did not cause significant decreases in synthesis at 0.1 mg/mL in the first days after exposure, followed by an increase in synthesis only between days 4 and 7 (Murphy et al., 2000). BTM was also investigated regarding its effects on PG synthesis in one study (Frean, Cambridge & Lees, 2002), where suppression was caused by higher concentrations (0.1–100 ?g/mL) with no significant changes at lower doses (0.001–0.05 ?g/mL) (Frean, Cambridge & Lees, 2002). Collagen synthesis was also evaluated for MPA, which significantly decreased at higher doses (Fubini et al., 2001).

PG degradation (i.e., PG released into the medium) was evaluated in four studies. Three evaluated the effect of MPA/MPS and found conflicting results. While no significant changes were found by Byron et al. (2008), increases in PG degradation were found by Murphy et al. (2000). Doyle et al. (2005) found that MPA had a positive effect by significantly decreasing the release of newly synthesized PG at one tested dose (5 mg/mL). BTM was evaluated in one study, which found significant increases in PG released into media at higher doses (Frean, Cambridge & Lees, 2002).

Total GAG content showed significant increases to no changes when MPA was applied (Doyle et al., 2005; Byron et al., 2008), and total cartilage DNA content showed no significant changes in response to MPA (Doyle et al., 2005; Byron et al., 2008), DEX, or TA (Busschers, Holt & Richardson, 2010).

Oxidative profile was evaluated in one study only, which investigated the TA treatment in normal cartilage explants. There were no differences in lipid peroxidation, activity of catalase, or glutathione peroxidase compared to controls (Palma et al., 2019a).

Gene expression changes

Gene expression of proteolytic enzymes, ECM components, and inflammatory proteins in normal cartilage explants/chondrocytes were also investigated after MPA/MPS, TA, and DEX treatments. MPA, DEX, and TA significantly collagen II expression in two studies (Fubini et al., 2001; Richardson & Dodge, 2003), while ACAN, biglycan, and decorin expression did not change after DEX or TA treatments (Richardson & Dodge, 2003; Palma et al., 2019b). For proteolytic enzymes, TA caused no significant changes in the study of Palma et al. (2019b), while Busschers, Holt & Richardson (2010), and Richardson & Dodge (2003) found significant decreases in MMP expression.

No significant changes were found for the expression or activity of inducible nitric oxide synthase, COX-2 expression, or PGE_2 concentrations in media after DEX treatments or oxidative profile and cell viability after TA treatments (Tung, Venta & Caron, 2002; Tung et al., 2002; Palma et al., 2019a).

Effects of different doses

Regarding dose effects, nine studies investigated the effects of corticosteroids at various doses. MPS/MPA and BTM had better results in healthy joint tissues when lower doses were employed, while results for DEX and TA were not unanimous (Murphy et al., 2000; Fubini et al., 2001; Frean, Cambridge & Lees, 2002; Doyle et al., 2005). DEX showed no dose effects in three studies and TA in one (Tung, Venta & Caron, 2002; Tung et al., 2002; Busschers, Holt & Richardson, 2010). One group showed better results for decreasing proteolytic enzymes with higher doses and better results for ECM components with lower doses for both corticosteroids (Richardson & Dodge, 2003).

DISCUSSION

IA corticosteroids have been the most used treatment for articular lesions for years; however, this is a controversial therapy. This systematic review gathered data regarding its effects on joints (McIlwraith & Lattermann, 2019; Velloso Alvarez et al., 2020; Boorman et al., 2022). The evidence suggests that 1) single IA corticosteroid injections in OA joints tend to show higher effectiveness in SMOA in studies with shorter follow-ups or at periods shorter than the follow-up proposed. DMOA showed no consistent adverse effects, varying according to corticosteroids. Nevertheless, some conflicting results were within the same corticosteroid type across studies. 2) Corticosteroids appear not to induce symptomatic changes in normal joints in horses, although adverse changes to joint tissues (cartilage or SM) and metabolism are usually found. A dose effect, where lower doses have better—or less detrimental—responses, was found in *in vitro* studies of normal equine articular tissues. The risk of bias in included studies was mainly unclear because the authors did not report the entire methodology. For example, it was not reported whether groups were randomized, and if so, what was the randomization method. Therefore, whether the study presents bias arising from selection, performance, detection, attrition, or reporting is unclear. Despite being implied at times, a clear description of methods should always be included, even if it sounds repetitive. Reporting guidelines for different study designs are currently available. By following these, authors can achieve a lower risk of bias, improving study quality and (consequently) reliable data.

A single injection of corticosteroids for OA joints was evaluated to answer question 1. Articles investigating such topics were more common in humans, where the primary outcomes were usually PROMs. SMOA effects tended to show improvements in shorter follow-ups, having positive effects reported in up to three weeks in horses (lameness) and 3–12 weeks in humans. Beyond this period, one study found detrimental effects to SMOA in horses (de Clifford et al., 2021), while in humans, drawbacks were limited to the loss of positive effects. Despite sharing similarities in the disease process, this finding may point to the possible divergent responses in different species and emphasizes the need for species-specific studies to ensure the application of findings in clinical settings.

Regarding DMOA changes after single injections in OA joints, outcome measures varied according to the corticosteroid; however, *in vivo*or clinical studies including these outcomes were more scarce than ones including SMOA effects. Findings usually represent changes in joint metabolism, indicating possible disease progression rather than linking the disease progression to corticosteroids. For example, changes from imaging tools were conflicting, ranging from significantly higher chances of joint deterioration to no significant risk of worsening of disease progression compared to controls (Okike et al., 2021; Latourte et al., 2022). A positive effect seen in radiographs was only found for TH in one study, in which patients showed disease progression at a significantly lower rate than controls (Nunes-Tamashiro et al., 2022). Other DMOA changes included SF WBC counts (conflicting results for TA with no changes for MPA), negative results such as increasing synthesis of smaller PG (MPA) inducing changes in chondrocytes phenotype (MPA), transiently increasing GAG concentrations in SF (TA), and increasing in PGE_2 concentrations in SF (TA). Positive DMOA were decreases in SF TP (TA), decreases in CCL2 and MMPs activity (TA), and improvements in SM immunohistochemistry (MPA). No other significant changes were found in DMOA of horses or humans injected with corticosteroids for OA treatment.

The effects of corticosteroid exposure on normal joints were also investigated. As expected for any therapy,

corticosteroids (MPA and TA) did not cause lameness or joint effusion when these were investigated in three studies (Murray et al., 1998; Robion et al., 2001; Céleste et al., 2005). However, some adverse effects on normal joints were found when MPA and TA were evaluated *in vivo* . Outcome measures were usually those that can demonstrate disturbances in homeostasis (WBC, TP, PG, GAG, and HA concentrations in SF, PG synthesis in cartilage, biomarkers, and gene expression in SF) while some also showed adverse changes in histology and histochemistry of SM and cartilage and biomechanics of cartilage (Frisbie et al., 1997; Murray et al., 1998; Frisbie et al., 1998). At such levels, more modest positive changes could also be found compared to controls (improvements in histology of cartilage and SM, GAG metabolism and synthesis for TA, improvements in collagen and protein synthesis in cartilage and SM, and increases in lubricating surfactant secretion for MPA). *In vitro* , adverse effects were common for all corticosteroid types (MPA, BTM, DEX, and TA). These included impairments of cartilage metabolism (synthesis and degradation) with usually dose-dependent effects, where lower doses were associated with less detrimental changes.

Effects of medications on normal joints are usually performed to assess the therapy's safety; however, findings are frequently extrapolated to clinical use in diseased joints. Although this makes sense, the environment of healthy and osteoarthritic joints is highly divergent; therefore, they may behave differently when exposed to therapy. For example, Todhunter et al. (1998) found that the inhibition of PG synthesis in healthy joints exposed to corticosteroids was not present in lipopolysaccharide-induced joints treated the same way. This finding was also seen in Frisbie et al. (1997), in which GAG content in SF was significantly higher in normal joints exposed to TA but not significantly different from controls when surgically induced joints were treated similarly. Accordingly, some differences in the effects of MPA in healthy and diseased joints were found by Frisbie et al. (1998). This finding suggests that results from normal and diseased joints differ and should not be considered together.

Limitations of this review include heterogeneity of included studies and employed treatment protocols, which hamper comparisons and unclear risk of bias for most of the results presented.

CONCLUSION

Evidence gathered in this review was mainly rated as unclear risk of bias. Our findings suggest that 1) single IA corticosteroid injections tend to show higher effectiveness in SMOA in studies with shorter follow-ups, while DMOA varied according to corticosteroid with conflicting results regarding the same type of corticosteroid across studies. 2) Corticosteroids do not induce symptomatic changes in normal joints of horses despite adverse effects on joint tissues and metabolism. This finding could indicate pathways that might lead to detrimental effects on joint health; however, direct changes are lacking. A dose-dependent effect, where lower doses have better—or less detrimental—responses, was found in *in vitro* studies of normal equine articular tissues.

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.

CONFLICT OF INTEREST

All authors on the paper declare no actual or potential conflicts of interest.

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Figure 1 . Flow diagram of the selection process of included studies for both questions of this review.

Figure 2. Risk of bias of included studies. A) Assessment through the Cochrane risk of bias tool for RCTs and pre-clinical in vivo studies with horses; 1 = Random sequence generation (selection bias); 2 = Allocation concealment (selection bias); 3 = Blinding of participants and researchers (performance bias); 4 = Blinding of outcome assessors (detection bias); 5 = Incomplete outcome data (attrition bias); 6 = Selective reporting (reporting bias); 7 = Other bias; FINAL = Final criteria of study; B) Assessment through the MINORs tool for observational studies.

Figure 3. Risk of bias of included studies for question 2. Assessment through the Cochrane risk of bias tool for pre-clinical*in vivo* studies with horses; 1 = Random sequence generation (selection bias); 2 = Allocation

concealment (selection bias); 3 = Blinding of participants and researchers (performance bias); 4 = Blinding of outcome assessors (detection bias); 5 = Incomplete outcome data (attrition bias); 6 = Selective reporting (reporting bias); 7 = Other bias; FINAL = Final criteria of study.

Table 1. Search strategy employed in each database.

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`Tables 1.docx` available at https://authorea.com/users/697850/articles/685842-a-comprehensive-systematic-review-of-intra-articular-corticosteroids-symptom-and-disease-modification-osteoarthritis-effects-and-the-potential-impact-on-healthy-joints-part-1