



FACTFINDERS FOR PATIENT SAFETY

THE POTENTIAL RISKS OF CHONDROTOXICITY FROM INTRA-ARTICULAR CORTICOSTEROID INJECTIONS

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MYTH: There is a definitive risk of chondrotoxicity from intra-articular corticosteroid injections.

FACT: While *in vitro* and *in vivo* studies suggest potential chondrotoxic effects associated with intra-articular injections that include corticosteroids, there is insufficient evidence to establish a definitive causal relationship between intra-articular injections of only corticosteroids and clinically significant chondrotoxicity.

Intra-articular corticosteroid injections (IACS) are commonly used for the treatment of symptomatic osteoarthritis and painful intrinsic joint pathology. Although the association between local anesthetics and chondrotoxicity is well established [1], less is known about the potential chondrotoxic effects of intra-articular corticosteroids. The purpose of this FactFinder is to examine the available evidence regarding this risk.

A review of *in vitro* studies by Wernecke et al. [2] showed a general trend of corticosteroid chondrotoxicity that was dose- and time-dependent, with higher doses and longer culture durations associated with increased cartilage damage. This was demonstrated with hydrocortisone, methylprednisolone, dexamethasone, prednisolone, betamethasone, and triamcinolone. A more recent review by Pirri et al. identified 33 papers examining corticosteroid chondrotoxicity *in vitro* and *in vivo* and reached a conclusion similar to that of Wernecke et al. regarding *in vitro* studies, but noted that triamcinolone may be the least chondrotoxic [3]. This was based on 6 *in vivo* studies (4 animal and 2 human) that did not demonstrate adverse effects of triamcinolone on cartilage [4-9]. Notably, 5 of the 33 papers included in this review assessed corticosteroid solutions combined with a local anesthetic agent. Not included in this review was a 2-year, randomized, placebo-controlled, double-blind trial of intra-articular triamcinolone vs. saline injections (neither group received local anesthetic) for symptomatic knee osteoarthritis in 140 patients [10], in which pre-procedure and annual magnetic resonance imaging (MRI) scans were used to assess progression of osteoarthritis. This study found greater cartilage loss in the triamcinolone group than in the saline group (between-group difference of -0.11 mm; 95% CI, -0.20 to -0.03 mm). However, the groups did not differ significantly in progression of cartilage denudation, bone marrow lesions, trabecular morphology, or effusion volume. The clinical significance of the relatively small change in cartilage thickness between groups is uncertain, as there were no significant between-group differences in knee pain, function, or the incidence of osteonecrosis or subchondral randomized, double-blind, placebo-controlled trial (n=68) included in the review by Pirri et al. found no difference between groups on standardized radiographs at 1- and 2-year follow-up. This may reflect MRI's greater sensitivity in detecting small changes in cartilage loss than plain radiographs, which detect only

joint space narrowing secondary to cartilage loss, as well as the smaller study's inadequate power to detect a significant between-group difference [9].

A 2024 double-blind, placebo-controlled trial compared baseline and follow-up MRI in 120 human knees with mild or moderate knee osteoarthritis (Kellgren-Lawrence grade 1-3), which received either 1 mL of triamcinolone (concentration not specified), 6 mL of hyaluronic acid (Suplasyn), or 3 mL of platelet-rich plasma (PRP). The placebo group received 1 mL of iopamidol contrast only. MRIs were obtained just before the intra-articular knee injection and at 3 and 12 months post-injection. Morphological parameters of cartilage degeneration did not change significantly at 3 and 12 months across all groups [11].

A particularly relevant measure of the clinical significance of chondrotoxicity is time to joint replacement. Latourte et al. [12] assessed the association between intra-articular knee joint corticosteroid injections and the 5-year risk of incident total knee replacement (TKR) or radiographic worsening in 564 patients from the French Knee and Hip Osteoarthritis Long-term Assessment cohort, which included a population-based cohort of 878 patients with symptomatic knee and/or hip osteoarthritis. They found that, compared with untreated knees, intra-articular knee joint corticosteroid injections were associated with a similar risk of incident TKR and radiographic worsening. The mean $\pm$ standard deviation of reported corticosteroid injections during the 5-year follow-up period was 1.9 $\pm$ 1.4. Limitations of this study include the relatively small number of patients who received corticosteroid injections ($n=51$), the absence of data on the type and dosage of corticosteroids used, and whether patients also received intra-articular local anesthetics.

Rapidly Progressive Osteoarthritis and Osteonecrosis

Although rapidly progressive osteoarthritis (RPOA) and osteonecrosis can occur in individuals with no history of intra-articular steroid injections, there is a concern that intra-articular steroid injections increase the risk of developing these conditions. RPOA and osteonecrosis are secondary conditions of particular concern, as these conditions can be associated with significant morbidity and necessitate the need for a joint arthroplasty. The use of the term RPOA within the literature is variable; however, two forms of RPOA have been described. RPOA Type 1, also known as accelerated osteoarthritis progression, refers to rapid loss of joint space beyond the expected rate, which some authors define as more than 2 mm of joint space loss within a 12-month period [13]. RPOA Type 2, also known as rapid joint destruction, includes bone loss and structural collapse atypical for osteoarthritis [13]. It has been proposed that this may be precipitated by an undiagnosed subchondral insufficiency fracture or attributed to accelerated osteonecrosis [13].

Osteonecrosis and avascular necrosis (AVN) are often used interchangeably, but the term "osteonecrosis" is considered more appropriate, as it is now viewed as the result of disrupted bone homeostasis arising from both vascular and nonvascular mechanisms [14].

A recent systematic review and meta-analysis by Sabatini et al. [15] looked at the incidence of rapidly progressive osteoarthritis following intra-articular hip corticosteroid injections. They identified only 10 studies (2 prospective, 8 retrospective) that both met their inclusion criteria and included follow-up imaging to detect rapidly progressive osteoarthritis. Their meta-analytic estimate of RPOA was 6% (95% confidence interval of 3%-9%); however, this may be an overestimate because of the varying definitions of RPOA (with some studies using definitions that may have represented the normal progression of osteoarthritis), and the preponderance of retrospective studies that may inherently have selection bias or confounding by indication. This review was also limited by including studies in which patients received a combination of corticosteroid and local anesthetic intra-articular injections.

Zhao et al. [16] recently performed a systematic review to assess the incidence of osteonecrosis following intra-articular hip corticosteroid injections. They identified 14 studies that met the inclusion criteria, comprising 7 case reports, 4 retrospective case series, and 3 retrospective cohort studies. These studies reported an incidence of osteonecrosis ranging from 0.6% to 20.4% following intra-articular hip joint corticosteroid injections. However, the authors acknowledged that drawing conclusions from this review was difficult because the available evidence was low quality and included no randomized controlled trials or prospective studies. It was also noted that there was significant variability in the utilized steroids in the included studies, and not all patients had pre-procedure imaging. The absence of pre-procedure imaging is particularly important to note, since patients with undiagnosed osteonecrosis may have been referred for treatment of osteonecrosis-related hip pain. Additionally, it appeared that all patients in the included studies received injections containing a combination of corticosteroid and local anesthetic.

Assessing RPOA and osteonecrosis risk is further complicated by the condition's heterogeneity and the varying definitions used in the literature. In reviews of both RPOA and osteonecrosis, many studies included patients without pre-procedure MRIs, which are necessary to exclude an early subchondral insufficiency fracture or early osteonecrosis that may not be apparent on X-ray. As a result, there is still insufficient evidence to support a causative relationship between intra-articular steroid injections and RPOA or osteonecrosis.

Discussion

Given the potential chondrotoxicity associated with IACS, there should be shared clinical decision-making with patients regarding the potential risks and benefits of these injections, and a discussion of alternative treatment options. This decision-making process is particularly important when considering IACS for painful intrinsic joint conditions other than osteoarthritis (e.g., labral tears, meniscal tears, adhesive capsulitis).

Kompel et al. also highlighted the concern of radiographically occult subchondral insufficiency fractures in individuals being considered for IACS, as this could potentially progress to RPOA if not appropriately treated [13]. Therefore, there should be a low threshold for considering a pre-procedure MRI for individuals with severe pain despite minimal osteoarthritis on radiographs, and for ordering repeat radiographs before subsequent injections when pain or function is notably worse than the initial presenting symptoms.

If IACS are utilized, it is recommended to use the lowest effective dose as infrequently as possible. A multisociety guideline published in 2025 [17] noted little evidence supporting one steroid over another, but identified the lowest effective dose as 20 mg of triamcinolone or methylprednisolone for glenohumeral joint injections and 40 mg for hip and knee joint injections. No recommendations were provided on the lowest effective dose for injections of other joints. It was also suggested that there should be a minimum interval of 2-3 weeks to 3 months between injections. However, these guidelines acknowledged that most respondents in a survey by the American Association of Hip and Knee Surgeons preferred a 3-month minimum interval between IACS in the same joint [18]. These recommendations do not apply to extended-release triamcinolone acetonide, a microsphere formulation indicated for knee osteoarthritis pain. The FDA-approved label for this medication indicates that the efficacy and safety of repeat administration have not been established, and it has not been evaluated for the treatment of osteoarthritis pain in the shoulder and hip. The label also states that this medication is not suitable for small joints, such as those in the hand [19].

Conclusions

- *In vitro* studies have demonstrated general trends indicating that corticosteroids exhibit dose- and time-dependent chondrotoxicity.
- *In vivo* studies have shown an association between intra-articular corticosteroid injections and direct chondrotoxicity, rapidly progressive osteoarthritis types 1 and 2, and osteonecrosis; however, evidence remains insufficient to establish definitive causation. The paucity of randomized controlled trials and prospective studies, the limited number of studies that include pre-injection MRI to exclude radiographically occult insufficiency fractures and osteonecrosis, and, perhaps most importantly, the frequent inclusion of patients who received combined corticosteroid and local anesthetic injections (local anesthetics also carry a risk of chondrotoxicity) all contribute to the inability to establish causation.
- Excluding cases of RPOA and osteonecrosis, any potential direct corticosteroid-associated chondrotoxicity does not appear to be clearly associated with worse clinical outcomes.
- There should be a low threshold for considering a pre-procedure MRI for individuals with severe pain despite minimal osteoarthrosis on radiographs, and for ordering repeat radiographs before subsequent injections when pain or function is notably worse than the initial presenting symptoms. This could help to screen for individuals with radiographically occult insufficiency fractures and osteonecrosis, and those developing rapidly progressive osteoarthritis.
- Given the potential for chondrotoxicity, if intra-articular corticosteroid injections are utilized, the lowest effective dose (as infrequently as possible) is recommended. Suggested doses are 20 mg of triamcinolone or methylprednisolone for glenohumeral joint injections, and 40 mg for the hip and knee joint injections. Clinical practice guidelines suggest a minimum interval of 2-3 weeks to 3 months between injections, but most respondents in a survey by the American Association of Hip and Knee Surgeons preferred a 3-month minimum interval between IACS in the same joint.

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