Injectable Corticosteroids: Take Precautions and Use Caution

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Abstract

Corticosteroids are routinely injected into soft tissues, tendon sheaths, bursae, and joints. These anti-inflammatory agents have different potency and solubility, and solubility is inversely correlated with the duration of action. Corticosteroids carry a low risk of complications but commonly cause systemic and local adverse effects. The use of intra-articular corticosteroid injections in the treatment of inflammatory arthritis and osteoarthritis is well established. Evidence also supports the use of injectable corticosteroids in the treatment of inflammatory tenosynovitis and bursitis associated with rheumatic diseases, trigger finger and de Quervain disease, and carpal tunnel syndrome. The role of corticosteroid injections in the management of rotator cuff disease remains unclear. Strong scientific evidence indicates that corticosteroid injections for lateral epicondylosis worsen the long-term outcomes of patients. This review article discusses the considerations related to the use of corticosteroid injections in the management of nonspinal musculoskeletal conditions.

Keywords
- corticosteroid
- intra-articular injection
- soft tissue injection
- tendinopathy
- musculoskeletal disorders

The advent of synthetic corticosteroids as anti-inflammatory therapy agents has been one of the great advances in medicine.[1] In 1951, Hollander et al[2] reported short-term alleviation of local symptoms and signs of synovial inflammation in a large series of patients with various rheumatic disorders treated with intra-articular hydrocortisone injections. For years to come, this report changed dramatically the clinical management of rheumatic diseases. Since then, physicians including radiologists have been routinely injecting corticosteroid preparations alone or in combination with local anesthetics to provide pain relief and local anti-inflammatory therapy in the management of various articular and soft tissue conditions.[3] Local anesthetics may be added to corticosteroid preparations to provide immediate short-term relief, to increase the volume and the dispersion of the injectate, or to provide diagnostic feedback by differentiating between local and referred pain.[4] In that regard, single intra-articular injections of lidocaine 1% or bupivacaine 0.25% without epinephrine have been shown not to affect the viability of articular chondrocytes and are considered to be safe.[5] With the wide use of injectable corticosteroids for localized conditions inevitably come adverse effects and the risk of complications.[6] Although corticosteroid injections are generally useful in the treatment of inflammatory arthritis[7] and osteoarthritis,[8] the value of these injections to treat overuse tendinopathies has been questioned.[9–11]

This review article provides an overview of the structure of corticosteroid preparations and discusses the potential adverse effects and complications, the contraindications, and the use of corticosteroid injections in managing nonspinal musculoskeletal conditions.

Pharmacology of Corticosteroid Preparations

Glucocorticoids and mineralocorticoids are steroid hormones released by the adrenal cortex.[12] Mineralocorticoids such as aldosterone regulate electrolyte and fluid balance. Glucocorticoids such as cortisol help control metabolism including glycemia, inflammation, and immune functions. Glucocorticoids predominantly target gene transcription related to

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inflammatory proteins and cytokines.[13] The result is a decreased vascular response, reduced accumulation of inflammatory cells, and downregulation of immune function. Prednisolone is a synthetic glucocorticoid and a derivative of cortisol, with predominant glucocorticoid and low mineralocorticoid effects from which injectable corticosteroids commonly used in radiology are derived. The pharmacodynamics of injectable corticosteroids are not completely understood. A local effect of decreasing inflammation in synovial or extra-articular soft tissue appears to be the main mechanism of action. Dose-related systemic effects are also likely to occur. The mechanisms underlying symptom relief following corticosteroid injections in noninflammatory overuse tendinopathy remain unclear.[14]

Based on their physical properties, injectable corticosteroids can be classified as soluble or insoluble in water (►**Table 1**). The acetate/acetonide formulations are insoluble because they contain steroid ester groups that lead to the formation of microcrystals in water. Because they require hydrolysis by cellular esterases to release their active fraction, ester preparations last longer at the injection site.[3] The sodium phosphate formulations are non-ester preparations that do not form particles and are soluble in water. These non-ester corticosteroids are readily available to cellular metabolism and therefore have a more rapid onset of action. Non-ester corticosteroid preparations have a potency about five times greater than that of ester preparations and require proportionally smaller injection doses to achieve an equivalent clinical effect. In vitro studies have shown considerable variation in the size of particles of different corticosteroid preparations and in their propensity to coalesce and form larger aggregates.[15–17] It is noteworthy that corticosteroid ester preparations generally harbor larger size particles with a variable tendency to form aggregates, whereas dexamethasone sodium phosphate does not form crystals. Although ester preparations may be equally suitable for intra-articular injections, a more water-soluble corticosteroid preparation or one that forms fewer crystal aggregates may be more appropriate for perineural and more superficial soft tissue injections, notably to decrease the risk of cutaneous atrophy and depigmentation. Benzyl alcohol and polyethylene glycol are two chemical agents commonly used in corticosteroid preparations as a preservative and as a drug vehicle, respectively. Although their potential adverse neurotoxic effects have been questioned, no definite link has been established, and at least one study showed that polyethylene glycol has no neurotoxic effects at a clinical concentration.[18] Mixing contrast material, corticosteroids (methylprednisolone acetate, triamcinolone acetonide) and local anesthetics (lidocaine, bupivacaine) is common practice when performing image-guided procedures, and indeed it has been shown not to alter the chemical stability of the compounds.[19]

Potential Adverse Effects and Complications

Intra-articular and soft tissue corticosteroid injections carry a low risk of serious complications but commonly cause systemic and local adverse effects[20] (►**Table 2**). Septic arthritis is the most feared complication following an intra-articular corticosteroid injection (►**Fig. 1**). However, when using an appropriate aseptic technique, the reported incidence is extremely low and has been estimated to be $\sim$ 0.01 to 0.03%.[7,21,22] Today, septic arthritis is a condition that is still generally associated with significant morbidity (31.6%) including osteomyelitis and deterioration of joint functional outcomes, and with relatively high mortality (11.5%).[23] Patients with rheumatic diseases, in particular rheumatoid arthritis, have an increased risk of infection compared with the general population, likely related to a state of immunodeficiency and the joint damage associated with the disease.[24,25] Papavasiliou et al suggested that the rate of iatrogenic infection following an intra-articular corticosteroid injection may be increased in patients who later require an arthroplasty.[26] Although these findings were not corroborated by other studies,[27–29] caution is advised when contemplating an intra-articular corticosteroid injection that will provide short-term symptomatic relief in a patient awaiting an elective arthroplasty.[22]

The most common adverse effect of intra-articular corticosteroid injections is postinjection flare, a local increase in inflammation that develops within hours following the injection and can last 2 or 3 days.[30,31] The inflammation may be caused by a sensitivity reaction to the steroid crystals or chemicals in the preparation. The reported incidence varies between 2% and 25%.[7] If the flare lasts $>$ 24 hours, joint aspiration is recommended to exclude infection. Iatrogenic adrenal suppression may occur following a single intra-articular or soft tissue corticosteroid injection and may last up to 2 weeks, putting patients at risk for an adrenal crisis in cases of trauma, infection, or surgery.[32] Therefore, patients should be advised to avoid activities that may be associated with extreme conditions such as heat, altitude, dehydration, athletic performance, or other situations at increased risk for trauma and infection such as sports or elective surgery, for a period of 2 weeks after a corticosteroid injection. Facial

Table 1 Physical properties of commonly used injectable corticosteroid preparations

Injectable corticosteroids	Chemical structure	Physical properties
• Methylprednisolone acetate • Triamcinolone acetonide • Betamethasone acetate	Ester preparations	• Highly insoluble in water • Form microcrystalline particulate suspensions • Slower release at the site of injection
• Dexamethasone sodium phosphate • Betamethasone sodium phosphate	Non-ester preparations	• Freely soluble in water • Nonparticulate (clear) preparations • Quicker onset of effect

Table 2 Adverse effects and potential complications of intra-articular and soft tissue corticosteroid injections

Adverse effects	Systemic	• Facial flushing • Hyperglycemic effect (in diabetic patients) • Adrenal suppression • Menstrual disturbances
	Local	• Postinjection flare • Postinjection pain • Subcutaneous atrophy • Skin depigmentation • Soft tissue calcifications
Potential complications	Local	• Tendon rupture • Articular hyaline cartilage damage • Septic arthritis

flushing is a common side effect of corticosteroid injections with a reported incidence of 10 to 15%,[33] and in our experience it tends to occur more frequently with triamcinolone acetonide and is dose related. Up to 36 hours after a corticosteroid injection, patients may experience redness of the cheeks and hot flashes that are generally self-limiting. The most likely pathophysiologic mechanism is a histamine-mediated response, and this adverse effect can be minimized with the use of antihistaminic medications taken before the injection.

Hyperglycemia occurs after corticosteroid injections in diabetic patients.[34] The increase in blood glucose levels is variable and transient and usually lasts for 2 to 5 days following a corticosteroid injection. Therefore, diabetic patients should be informed of this common side effect and advised to monitor their glycemia until it has normalized. Menstrual disturbances are a potential side effect associated with oral corticosteroid administration, and although their occurrence following an intra-articular injection has been suggested,[35] this has not been substantiated by controlled studies.

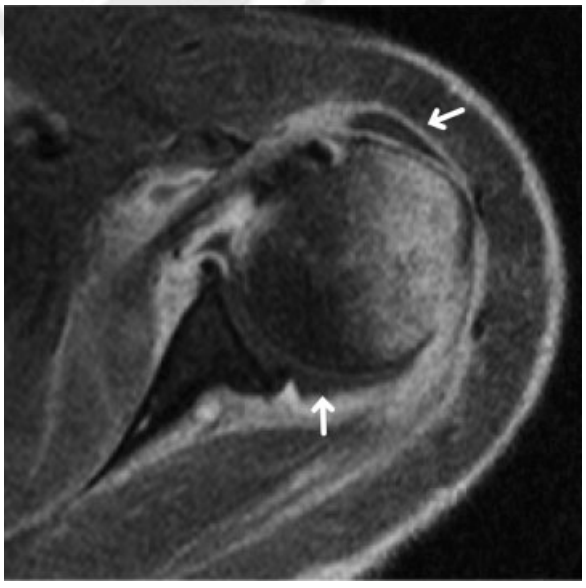

Fig. 1 A 63-year-old woman with bacterial septic arthritis of the left shoulder following fluoroscopy-guided corticosteroid injection. Axial T1-weighted fat-suppressed image of the left shoulder after intravenous gadolinium injection shows intense synovial, bursal, and bone marrow uptake and a small amount of joint (long arrow) and bursal (short arrow) fluid. Ultrasound-guided joint aspiration was performed. *Staphylococcus aureus* was confirmed as the offending organism.

In 2010, a systematic review examining the efficacy and safety of corticosteroid injections for the management of tendinopathy reported the following rates of adverse effects of 416 participants: 31% had postinjection pain, 9% presented subcutaneous atrophy, and 1% had skin depigmentation, whereas Achilles tendon rupture occurred in $< 1\%$ of cases.[10] It is noteworthy that methylprednisolone, which is more soluble than triamcinolone, was associated less with these adverse effects than triamcinolone and therefore may be the preferred preparation when injecting superficial structures. In 1984, Gilsanz and Bernstein reported an incidence of $\sim 30\%$ of periarticular calcifications following intra-articular corticosteroid injections in a series of patients with juvenile rheumatoid arthritis.[36] The patients appear to have been injected with triamcinolone hexacetonide, which has a lower solubility than the more commonly used triamcinolone acetonide[37] and is associated with an increased risk of soft tissue necrosis when injected outside a joint.[7] These calcifications were generally asymptomatic, and their location was related to the site of injection. In our experience, the occurrence of soft tissue calcifications following intra-articular and soft tissue corticosteroid injections is uncommon, and two systematic reviews on the adverse effects of extra-articular corticosteroid injections do not mention calcifications as side effects,[10,20] suggesting that this side effect may be related to the use of triamcinolone hexacetonide.

The results of animal studies on the potential effects of intra-articular corticosteroid injections on hyaline cartilage were inconclusive with some studies showing negative effects[38–40] and at least one study showing a protective effect.[41] Therefore, definite data on this issue have yet to be clearly demonstrated.[42] Large patient group studies have estimated the risk of substantial cartilage loss after repeated intra-articular corticosteroid injections to be low, $\sim$ 0.7 to 3%,[43,44] whereas one randomized controlled trial showed no deleterious effect of corticosteroid injections on articular cartilage at 2 years.[8] Finally, the evidence tends to suggest that the benefit of healing active synovitis, which leads to clinical improvement, outweigh the potential harm of corticosteroid injections on hyaline cartilage.[8,43] The medical literature does not provide a precise estimate of the incidence of tendon rupture following peritendinous corticosteroid injections, but numerous reports of such complications have been published.[45] Studies by Wong et al on the effects of dexamethasone and triamcinolone on cultured human tenocytes[46,47] and on tendon explant cultures[48] showed that glucocorticoids in in vitro conditions reduce cellular activity and collagen production. In vivo studies showed increased collagen disorganization and necrosis and reduced mechanical properties of tendon associated with local administration of corticosteroids.[49] Tendon rupture following local administration of corticosteroid was reported in the Achilles and patellar tendons, the common extensor and flexor tendons at the elbow, the extensor

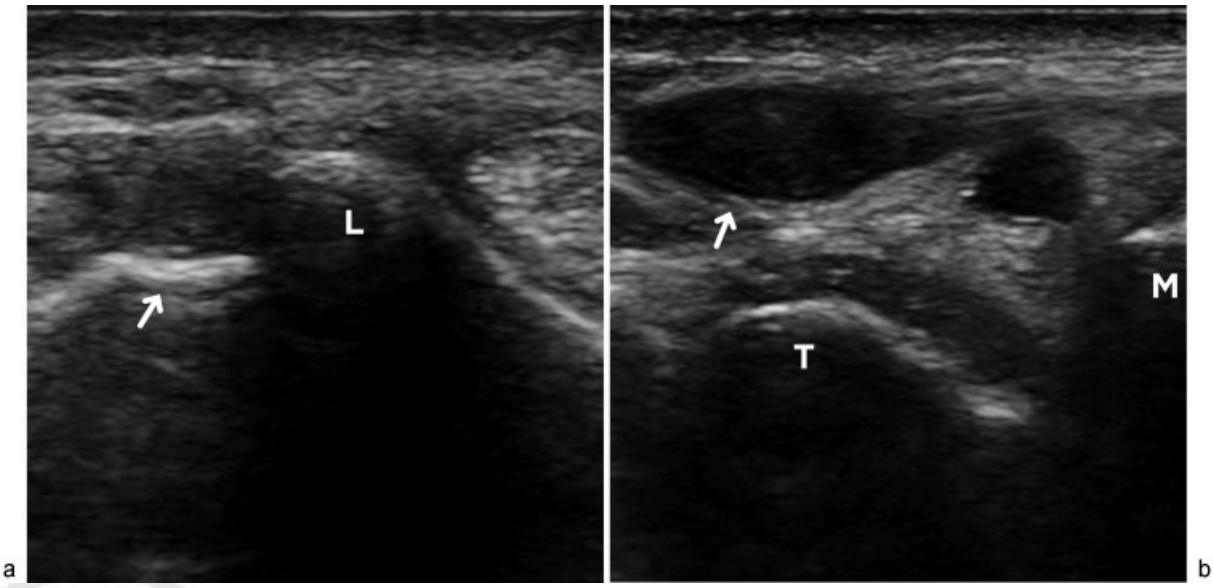

Fig. 2 A 56-year-old professional cook with a tear of the right extensor pollicis longus (EPL) tendon 1 month following an ultrasound-guided corticosteroid injection. (**a**) The EPL tendon is not visualized at its expected location in the third extensor compartment (arrow) adjacent to Lister tubercle (L). (**b**) The distal EPL tendon stump is located at the level of the trapezium (T) and appears hypoechoic and swollen (arrow). M, first metacarpal.

pollicis longus (►**Fig. 2**), and the tibialis anterior tendons,[50,51] and it can occur after a single injection.

Contraindications to Local Injection of Corticosteroids

Local administration of corticosteroids should not be performed in cases of sepsis or bacteremia or with local skin or periarticular soft tissue infection to avoid contaminating an aseptic compartment such as a joint or a tendon sheath. A joint injection should be avoided in the presence of an intra-articular fracture because corticosteroids inhibit bone healing.[52] Nonspinal articular and soft tissue injections are associated with a very low risk of bleeding and therefore can be performed in patients on anticoagulants and antiplatelet therapies.[53]

Use of Corticosteroids in Musculoskeletal Disorders

Articular Diseases

The use of intra-articular corticosteroid injections as an adjuvant therapy in the treatment of inflammatory arthritis[54,55] and knee and hip osteoarthritis[56–59] is well established, and it may help preserve the integrity of the joint.[60] Intra-articular corticosteroid injections generally provide short-term pain relief and functional improvement,[61,62] although there is great variability in the duration and magnitude of the clinical response. In a longitudinal cohort study, an intra-articular corticosteroid injection guided by computed tomography provided significant clinical improvement at 6 months in active sacroiliitis in patients with spondylarthropathy.[63] The presence of an effusion in knee and hip osteoarthritis was cited as a predictor of pain relief,[64] but the determinants of a positive response to an intra-articular corticosteroid injection remain incompletely understood.[65] Furthermore, the clinical benefit of performing a fluid aspiration before a corticosteroid injection when an effusion is present remains unclear.[65] The literature on osteoarthritis generally recommends that the interval between intra-articular corticosteroid injections be at least 4 to 6 weeks, and the number of injections at one site should be limited to three or four per year to minimize the potential deleterious effects of corticosteroids on articular structures.[7,8] However, these recommendations are mostly empirical. Moreover, definite guidelines on the most appropriate dosage and the most effective type of corticosteroid preparations for intra-articular injections are lacking. Some evidence indicates that triamcinolone is more effective than other corticosteroids.[66] For knee injection, 40 mg triamcinolone acetonide appear to be an effective dose.[6,8] The benefit of intra-articular corticosteroid injections in the treatment of osteoarthritis of smaller joints is less clear. In a controlled randomized trial, no clinical benefit of intra-articular corticosteroid injections was achieved in moderate to severe trapeziometacarpal osteoarthritis compared with a placebo.[67] Another randomized controlled trial compared the effect of blind intra-articular triamcinolone hexacetonide/lidocaine injection with lidocaine injection alone for the treatment of the most symptomatic interphalangeal joint of the hand and found no difference between the groups relative to pain at rest.[68]

Tendon Disorders

The spectrum of tendon disorders includes lesions of the paratenon and tenosynovial sheath, the enthesis, and the tendon proper.[69] Lesions may coexist, and the tendon may also tear partially or completely. Inflammatory tenosynovitis (and bursitis) associated with rheumatic diseases such as rheumatoid arthritis, psoriasis, and other spondyloarthropathies, similarly to articular synovitis, responds favorably to corticosteroid injections.[70] In our experience, intrasheath ultrasound-guided injections of even very small doses of

corticosteroids (8 mg methylprednisolone) is very efficient at treating proliferative tenosynovitis in the hands, ankles, and feet. To minimize the potential adverse effects of corticosteroids on the tendon, care should be taken to avoid an intratendinous injection, and a more soluble corticosteroid preparation is recommended as well as relative rest of the affected area for 2 weeks following the injection, but these recommendations are anecdotal and not based on scientific evidence.[69]

Histopathologic findings in chronic stenosing tenosynovitis indicate morphological alterations of chronic inflammation and fibrotic changes that impair the gliding function of the tendon sleeve.[71] Because of their anti-inflammatory and antiproliferative effects, using corticosteroids as part of the treatment strategy in stenosing tenosynovitis of the flexor tendons of the hand (trigger finger) and first compartment extensor tendons of the wrist (de Quervain disease) appear justifiable as first-line interventions, and the efficacy and safety of corticosteroid injections in those clinical situations are supported by clinical evidence including two randomized clinical trials.[72,73] Other observational studies reported long-term remission of symptoms in at least 69% of patients with trigger finger[74] with treatment efficacy even higher when treating the thumb compared with other digits.[74–76] Younger patients and insulin-dependent diabetic patients are more likely to have recurrence of symptoms.[77]

The physiopathology of chronic tendinosis and insertional tendinosis commonly seen in different locations including the extensor and flexor tendon origins at the elbow, the gluteus medius and minimus tendon origins at the greater trochanter, the tibialis posterior, and the Achilles tendons involves mechanical overuse and overload repetitive insults, degenerative changes, and a failed healing response but no cellular evidence of inflammation.[71,78,79] Therefore, the use of corticosteroids in the treatment of these painful tendon conditions seems counterintuitive. Not surprisingly, clinical evidence shows that corticosteroids reduce pain in the short term (4–12 weeks) compared with other nonsurgical interventions, but the tendency is reversed in the intermediate term (13–26 weeks) and long term (> 52 weeks).[10] The effect of corticosteroids varies between sites of tendinosis but has been particularly well studied in the case of chronic lateral epicondylosis of the elbow.[9,10,80] A placebo-controlled study demonstrated poorer long-term outcomes and a higher recurrence rate at 1 year after a corticosteroid injection to treat lateral epicondylosis.[9] Furthermore, this study refutes the notion that corticosteroid injections may assist active rehabilitation. In view of the cumulative evidence, many authors advocate that use of corticosteroids to treat lateral epicondylosis should be strongly discouraged.[9,11,81]

Insertional gluteal tendinosis commonly referred to as greater trochanteric pain syndrome is characterized by chronic lateral hip pain and is most prevalent in middle-age to elderly women. A single ultrasound-guided corticosteroid injection in the greater trochanter bursa has been shown to provide substantial improvement at 4 weeks,[82] but the recurrence rate is high and scientific evidence on the optimal management of this pathology is lacking.[83]

Rotator cuff disease is a complex entity because different structures including the rotator cuff tendons, the long head of the biceps tendon, and the subacromial bursa may be involved alone or in combination. The pathophysiology encompasses tendinosis, partial or complete tendon tears, subacromial bursitis, impingement and altered biomechanics, and an end-stage disease of cuff arthropathy.[84] Therefore, there may be wide heterogeneity in clinical presentation, and identifying the source of pain may be difficult. This heterogeneity in clinical presentation is reflected in the inclusion criteria in clinical studies and may be a reason why evidence for the benefit of corticosteroid injections in rotator cuff disease remains unclear.[10,80,85] Blind versus image-guided subacromial bursa corticosteroid injections may be another issue in clinical trials contributing to the lack of definite evidence supporting the role of corticosteroid injection in the treatment of rotator cuff disease because blind injections were shown to be less accurate.[86,87]

Carpal Tunnel Syndrome

Corticosteroid injections are effective at decreasing symptoms of idiopathic carpal tunnel syndrome in the short, intermediate, and long term,[88–90] although surgery was shown to be somewhat more effective than corticosteroid injections at 2-year follow-up.[91] Corticosteroids may reduce perineural inflammation or soft tissue swelling within the canal, thus relieving mechanical compression and reverting ischemic factors that affect the median nerve.[92]

Conclusion

Judicious use of injectable corticosteroids is beneficial to the management of various nonspinal musculoskeletal disorders including rheumatic diseases, osteoarthritis, and certain tendon and nerve pathologies. Conversely, use of corticosteroid injections for the treatment of lateral epicondylosis should be discouraged. Using image guidance when performing corticosteroid injections and taking certain precautions may increase their effectiveness and reduce the risk of adverse effects.

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