

Looking Back: Safety of Current Treatments



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The clinical use of corticosteroid, viscosupplementation, and local anesthetic injections for intra-articular musculoskeletal pathologies remains a popular treatment option. For patients, these options offer a low-risk, minimally invasive, pain-relieving solution for a variety of joint-related complaints. For clinicians, injections often provide diagnostic information in addition to providing therapeutic benefit to the patient. In general, intra-articular injections are considered safe with a low-risk profile; however, adverse events have been reported, and it is critical for patients to understand all possible outcomes after an injection, including complications. In this article, we provide an overview of several common injectable agents for the treatment of musculoskeletal injuries and pathologies, with a special focus on the safety profile of corticosteroids, viscosupplementation, and local anesthetic agents.

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Introduction

By the year 2030, it is projected that 67 million adults in the United States will have a diagnosis of arthritis, with 25 million having significant activity limitation.¹ With a growing generation of individuals, who wish to remain as active through their fourth to sixth decades, there is an increased need for the use of nonoperative management of symptomatic joint pain.² The use of injections, including steroids, viscosupplementation, and local anesthetic agents, for the treatment of a wide variety of intra-articular musculoskeletal pathologies, including arthritis, has become increasingly popular. Injections are considered effective treatments for a variety of reasons. In most cases, intra-articular injections offer a low-risk, minimally invasive, pain-relieving solution, regardless of the underlying diagnosis. In many cases, injection-based treatment provides an option for patients who wish to avoid surgery, as well as for those with contraindications to operative management, and patients who have tried and failed other conservative treatment options.³ Despite the widespread use of injections for musculoskeletal

pathologies, there are several potential downsides associated with their use, including cost, lack of concrete clinical evidence supporting their use, and the often-unknown duration of efficacy. Although complications associated with injection-based therapies are rare, adverse events have been reported. The purpose of this article is to *look back* at several common injection-based therapies, including corticosteroids, viscosupplementation, and local anesthetic agents, with a specific focus on their safety profiles and potential-associated complications. Although intra-articular injections are used for a wide variety of pathologies, including but not limited to meniscus tears, chondral lesions, and ligament strains, they are most commonly employed for the treatment of pain and inflammation related to osteoarthritis and other forms of arthritis (ie, inflammatory arthritis), and thus for the purposes of this article, the authors will focus on the use of injections for an underlying diagnosis of arthritis.

Intra-Articular Corticosteroid Injections

The use of intra-articular glucocorticoid injections for the management of symptomatic arthritis was first described in the 1940s, with the first studies published in the 1950s, and 1960s,⁴⁻⁹ and it remains a mainstream treatment for millions of patients.¹⁰ Although not entirely understood, the mechanism of action of corticosteroids for the symptomatic relief of

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arthritis-related pain is thought to involve a local decrease in inflammation of the synovial tissues and inflammatory cell load, stimulation of fibroblast, and blood vessel formation, as well as stimulation of collagen repair.¹⁰⁻¹²

Although multiple studies have demonstrated glucocorticoid injections to have a clear benefit over placebo controls with respect to reducing pain and swelling, there has been little research on the short- and long-term toxicity and safety of these injections. As such, the true incidence of steroid-based injection complications is difficult to determine. In addition, multiple different glucocorticoid agents are available, each with different strengths, potencies, solubilities, and safety profiles. Further, clinicians often differ in the dose of steroid use as well as in the amount of local anesthetic given at the time of injection. Thus, it is difficult to interpret literature reporting on the efficacy and safety of "steroid injections" owing to the substantial variability in which these injections are administered. Some of the more common injectable glucocorticoids include methylprednisolone acetate (Depo-Medrol) and triamcinolone acetonide (Kenalog). Other agents include triamcinolone hexacetonide (Aristospan) and betamethasone sodium phosphate (Celestone phosphate). Kenalog and Aristospan are less soluble compared with Depo-Medrol, and are thus longer-acting agents.¹³

Although rare, several adverse reactions associated with intra-articular corticosteroid¹⁴ injections have been reported in the literature, including septic arthritis, nerve and blood vessel damage, postinjection symptom flair, synovitis, flushing, anaphylaxis, steroid-induced arthropathy, and systemic effects.^{3,10,11,14-16} Fortunately, owing to the overall low complication rate combined with reproducible pain reduction and symptom improvement, steroid injections have continued to be a mainstay of therapy for arthritis and other intra-articular pathologies. Notably, in 2002, the American College of Rheumatology guidelines for the management of rheumatoid arthritis deemed that corticosteroids were a safe option for the treatment of arthritis when administered by an experienced physician.¹⁷

Infection is, perhaps, the most serious potential complication associated with intra-articular corticosteroid injections. It has been reported that the incidence of septic arthritis after corticosteroid injections ranges from 1 per 3000 to 1 per 50,000 per year.^{6,18,19} In general, risk factors for septic arthritis are diabetes mellitus, rheumatoid arthritis, advanced age, immunodeficiency, recent joint surgery, joint prostheses, and skin infections,^{20,21} though little is known about which specific risk factors predispose patients to septic arthritis from intra-articular corticosteroid injections.

The risk of infection after intra-articular corticosteroid injections may not be limited to the immediate postinjection period. Specifically, some authors have suggested that intra-articular corticosteroid injections may predispose patients to infection when subsequently undergoing ipsilateral joint arthroplasty.²²⁻²⁹ The literature on this topic is mixed, likely owing to the multifactorial nature of periprosthetic joint infection development. In an effort to summarize the available literature on the topic, Charalambous et al²⁴ reviewed 8 hip and knee arthroplasty studies, and found that prior ipsilateral

joint injections had no significant effect on deep or superficial infection rates associated with subsequent arthroplasty.

One of the most frequently discussed potential complications of intra-articular corticosteroid injections is the progression of joint degradation.^{3,15} The proposed mechanisms of joint degradation related to repeated steroid injections include (1) increased wear of the diseased joint owing to an increase in activity corresponding with a reduction in symptoms, and (2) the potential for a catabolic effect of the corticosteroid on the articular cartilage. The latter mechanism has been evaluated in animal models, but has not been well studied in human models.^{11,30} Interestingly, some *in vitro* studies have assessed the chondrotoxicity of several types of corticosteroids, and have concluded that there is a relationship with chondrocyte death,^{31,32} but again, no correlation with clinical outcomes has been made. Clinical data looking at the effects of intra-articular corticosteroids on joint structure and cartilage have shown minimal differences when comparing steroid injections with saline (placebo) injections. Raynauld et al³³ conducted a double-blind randomized control trial of 68 patients with osteoarthritis of the knee receiving intra-articular knee injections of either 1 mL of 40 mg of triamcinolone acetonide or 1 mL of saline every 3 months for 2 years. The authors found no difference between the 2 treatment groups radiographically at 2 years, suggesting no effect of the steroid on joint deterioration.

Other complications associated with intra-articular corticosteroid injections include pain or swelling at the site of injection, localized erythema, skin and fat atrophy, and facial flushing.^{10,11} Postinjection pain is the most common overall reported complication of intra-articular steroid injections, thought to occur in 2%-10% of patients. Fortunately, the pain is transient, typically lasting no more than 2-3 days after the injection.^{2,3} Postinjection flair is a type of synovitis that is believed to be because of a chemical response from the injected steroid crystals.³⁴ This is nearly always transient in nature, and is effectively managed with oral nonsteroidal anti-inflammatory medications (NSAIDs) and cryotherapy.^{3,11} Skin and fat atrophy surrounding the injection site has been reported to occur in 0.6%-8% of patients, and can last for months after the injection. Skin depigmentation at the injection site is less common, occurring in <1% of patients and can be permanent.^{10,11,16,35} Facial flushing is another described adverse event associated with intra-articular injections, with a typical incidence of 0%-15%.^{3,10,11,15} Flushing has been found to occur more commonly in women and can be reduced by avoiding high doses of steroids.¹⁵

One of the more commonly asked questions regarding corticosteroid injection safety is how frequently corticosteroid injections can be given in a particular joint without causing joint damage. Unfortunately, the evidence surrounding the maximum safe frequency of intra-articular injection administration is limited, and thus no formal guidelines are available. Some authors suggest limiting injections to no more than 4 per joint per year owing to concern for joint deterioration; however, as mentioned in the previous section, the basic science correlating glucocorticoid injections to joint deterioration is limited.

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