

CLINICAL PERSPECTIVES

Corticosteroid Injections and COVID-19 Infection Risk

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Myth: Epidural and intra-articular steroid injections have no effect on the risk of contracting COVID-19 infection.

Fact: There is low-quality evidence that a single intra-articular corticosteroid injection may increase the risk of contracting the influenza virus. No study has yet been published that examines whether a corticosteroid injection increases the risk of contracting COVID-19 or alters the clinical course of a subsequent infection. While caution is advised based on this indirect evidence, more studies are needed to determine full correlation of corticosteroid administration and risks of contracting COVID-19.

The coronavirus disease 2019 (COVID-19) pandemic has forced the world's health care systems to reevaluate many previously held conventions and policies. This FactFinder will focus on the advisability of performing routine epidural steroid injections during a global viral pandemic and identify some of the relevant operational questions.

The Centers for Disease Control and Prevention (CDC) has identified a subset of the population that is at higher risk for severe illness when contracting COVID-19 infection [1]:

- People over the age of 65
- People who live in nursing homes or long-term care facilities
- Other high-risk conditions include the following:
 - Chronic lung disease

- Diabetes mellitus
- Heart disease
- Obesity
- Immunocompromised state

Systemic Corticosteroid Effects on Immune Cell Function

Therapeutic corticosteroids have wide-ranging physiologic effects [2]. The effect of systemic corticosteroids on immune system “compromise” is known. Dr. Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases since 1984 and one of the leaders of the US Coronavirus Task Force, published a seminal article on the subject in 1976 [3]. The human immune system can be simplified into two arms: 1) the innate immune system and 2) the adaptive immune system. The innate immune system is composed of neutrophils, macrophages, monocytes (collectively referred to as phagocytes), and mast cells, which react to foreign pathogens within minutes to hours. Mobilization of these cells is aided by complement activation and cytokines but does not require the presentation of an antigen and does not lead to immunological memory. The adaptive immune system, composed of lymphocytes, precisely recognizes unique antigens through cell surface receptors. The adaptive immune system is activated when the innate immune response is insufficient to control an infection. Systemic corticosteroid therapy may adversely affect both the innate

and adaptive immune response. The ability of neutrophils to migrate to sites of infection is impaired by corticosteroids [4]. Macrophage and monocyte function may also be inhibited by corticosteroids [5]. The capability of plasma cells (terminally differentiated B-lymphocytes) to produce immunoglobulins IgG and IgA is reduced 10–20% by corticosteroids [6]. Alternatively, a small body of literature indicates that corticosteroids may enhance the innate immune response in the epithelium in certain regions [7]. However, the balance of corticosteroid effects is generally considered to impair the immune response. This literature describes the effects of oral and other forms of systemic corticosteroid administration; the exact correlation to injection therapy is unknown, yet plausibly has similar effects.

Epidural Corticosteroid Injections Have Systemic Effects

Epidural corticosteroid injections are known to cause remote perturbations of the endocrine system and suppression of the hypothalamic–pituitary–adrenal axis (HPA). Habib et al. examined the magnitude and duration of HPA axis suppression following epidural injection. Injection of 80 mg of methylprednisolone resulted in a greater percentage of participants with laboratory-confirmed HPA axis suppression (86%) compared with a 40-mg dose (53%) at one week postinjection. Twenty percent of participants demonstrated continued HPA axis suppression at four weeks [8]. Longer-acting agents (triamcinolone and methylprednisolone) suppress cortisol production for a longer duration than more soluble agents (dexamethasone and betamethasone) [9]. Abdul et al. reported HPA axis suppression in 87% of participants seven days postinjection, 43% at day 14, and 7% at day 28 following epidural injection of 80 mg of methylprednisolone. The median (interquartile range) serum cortisol level at baseline and on days 7, 14, and 28 after intervention was found to be 329.55 (208.49–399.48) nmol/L, 72.99 (52.95–119.82) nmol/L, 194.45 (73.88–292.52) nmol/L, and 302.56 (257.68–357.43) nmol/L, respectively [10]. Iranmanesh et al. reported laboratory-confirmed suppression of adrenocorticotropic hormone (ACTH) and cortisol for one to four weeks and suppression of urinary free cortisol for more than 12 weeks following ESI with triamcinolone 80 mg [11]. Additionally, patient variables, comorbidities, and certain medications can significantly affect the magnitude and duration of HPA axis suppression. Systemic effects of epidurally administered corticosteroids are inadequately studied and underappreciated [12]. The known protracted dysfunction of the endocrine system from a single epidural steroid injection suggests that parallel systemic effects on the immune response are likely, though this has not been directly studied.

Intra-articular Corticosteroid Injections Have Systemic Effects

Intra-articular corticosteroid injections are known to have systemic endocrine effects similar to those of epidural corticosteroid injections. Following a single intra-articular steroid injection, serum cortisol (and the HPA axis) is significantly suppressed for one to four weeks, and in some cases much longer [13, 14]. Even a relatively low-dose triamcinolone (20 mg) intra-articular injection influences the HPA axis for one to two weeks. In the published literature, the percentages of study participants with diminished serum cortisol and the duration of suppression with either an epidural steroid injection or an intra-articular steroid injection are virtually identical.

Systemic Corticosteroid Increases Infection Risk

Study of oral corticosteroid vs placebo with meta-analysis demonstrates an increased risk of infection within the steroid group. One study reported a relative risk (RR) of 1.6 for participants taking >10 mg prednisone per day or a cumulative dose >700 mg [15]. A dose-dependent relationship was also observed for infection risk, which increased from an RR of 1.5 with low doses to >8 with doses >40 mg/d [16]. Among patients with rheumatoid arthritis on oral prednisone, the RR of hospitalization for pneumonia ranged from 1.4 (<5 mg/d) to 2.3 (>10 mg/d) when compared with patients not taking oral prednisone [17]. An oral dose of 10 mg of dexamethasone is equivalent to 62 mg of oral prednisone. It remains unknown whether single-dose epidural injection of a corticosteroid exerts an effect on the immune system similar to that of chronic oral administration.

Early evidence of the potential effect of single-dose corticosteroid exposure is described in a report on an observational cohort from the Mayo Clinic. This study investigated the association of a single intra-articular corticosteroid injection with increased risk of influenza infection [18]. Over a period of five influenza seasons, the rate of influenza infection was compared in vaccinated patients who had received an intra-articular corticosteroid injection vs those who had not. Joints were injected with a variety of products: betamethasone, methylprednisolone, and triamcinolone. The average cumulative dose given was 65.9 mg methylprednisolone equivalence (40–120). An increased incidence of influenza infection was associated with steroid injection compared with no injection (RR = 1.52, 95% confidence interval = 1.2–1.93). The CDC estimates that the common influenza vaccine is generally effective in reducing the risk of infection in the overall population by 40–60% [19]. While acknowledging the limitations of the study, these results suggest that, even among vaccinated individuals, an intra-articular corticosteroid injection before or during flu season may cause increased risk of infection. Whether this applies to single low-dose epidural administration remains untested.

Are Corticosteroid Injections for Pain Advisable During COVID-19?

During a global pandemic, it is tempting to focus efforts on mitigation and treatment of viral infection; however, all of the usual health problems not related to COVID-19 continue to exist. While limiting the spread of COVID-19 and preserving health care resources are of utmost concern, there may be times when interventional pain procedures may still be indicated [20]. The Centers for Medicare & Medicaid Services recognizes the problem of treating painful conditions during the pandemic and has registered severe pain as a tier IIIa category for which treatment can proceed [21]. Regional COVID-19 penetration, location of service (office/surgery center/hospital), and availability of personal protective equipment (PPE) may all be important factors to consider when scheduling an injection treatment. Severe pain, in itself, may impede the immune system, and undertreatment of postoperative pain, at least, has been associated with increased infection risk [22]. Bridging severe radicular pain with opioids until interventions revert back to usual may be counterproductive for a number of reasons, including the view that opioids themselves are a risk factor for increased susceptibility to infection through an independent immunosuppression mechanism [23]. There are no studies investigating the relationship between intra-articular or epidural corticosteroid injections and COVID-19 infection rate or severity of illness.

Key Points

1. Epidural and intra-articular corticosteroid injections have systemic effects.
2. No study has yet been published that examines whether a corticosteroid injection increases the risk of contracting COVID-19 or alters the clinical course of a subsequent infection. While it is plausible that single-dose corticosteroid exposure, including via intra-articular or epidural administration, could increase the risk for severe illness when contracting COVID-19 infection, there is insufficient evidence from which to draw definitive conclusions.
3. If considering corticosteroid administration, all patients should be counseled regarding the potential immunosuppression risks of corticosteroid injections, especially in the current setting of the COVID-19 pandemic. Patients who otherwise would be candidates for an intervention, once informed of the theoretical exposure risk, may self-select to defer and delay until they feel conditions are more conducive.
4. Candidates for corticosteroid injections during the COVID-19 pandemic whose pain is relatively controlled and deemed “nonemergent or nonessential” should be counseled to defer until after the pandemic subsides, if possible.
5. Corticosteroid immunosuppression appears to be dose-dependent; lower doses may mitigate the risk of immunosuppression.
6. Dexamethasone has been shown to have a shorter duration of systemic effect and may be favored over other steroids for injections in certain circumstances.
7. For continuous updates, refer to <https://www.spineintervention.org/page/COVID-19>.

For continuous updates and guidance from the Spine Intervention Society, refer to <https://www.spineintervention.org/page/COVID-19> [24].

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Teaching Images

OXFORD

Acute Calcific Tendinitis of the Longus Colli

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A 64-year-old man presented to the emergency department with a chief complaint of neck pain, dysphagia and mild fever (37.8°C) with onset two days prior. Laboratory tests revealed an elevated erythrocyte sedimentation rate of 68 mm/h, C-reactive protein of 113 mg/L and white blood cell count of 11,800/mL, which were suggestive of acute inflammation. Plain radiograph showed pre-vertebral soft tissue swelling in the C1-5 region (Figure 1). Life-threatening conditions such as retropharyngeal abscess, trauma, and cervical disc herniation were included in the differential

diagnosis. Laryngoscopy was performed, and a patent airway with no drainable abscess was observed. Noncontrast computed tomography showed amorphous calcification anterior to the C1-2 level, thickening of the prevertebral soft tissue and no evidence of abscess formation. Contrast-enhanced magnetic resonance imaging revealed a fluid collection within the prevertebral soft tissue (Figure 2). These radiologic findings are pathognomonic of acute calcific tendinitis of the longus colli (ACTLC) [1].