

Corticosteroid Injections and COVID-19 Infection Risk

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

Fact: There is low quality evidence that a single intraarticular corticosteroid injection may increase the risk of contracting the influenza virus. No study has yet been published that examines whether or not 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 healthcare 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 facility
- 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 U.S. National Institute of Allergy and Infectious Diseases since 1984 and one of the leaders of the U.S. 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 adaptative immune system. **The innate immune system** is composed of neutrophils, macrophages, monocytes (collectively referred to as phagocytes), and mast cells, which reacts 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 the 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 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 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 axis (HPA). Habib *et al.* examined the magnitude and duration of HPA 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 to a 40 mg dose (53%) at one-week post-injection. 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 post-injection, 43% at day 14, and 7% at day 28 following epidural injection of 80 mg of methylprednisolone. The median interquartile range (IQR) serum cortisol level at baseline and on days 7, 14, and 28 after intervention were 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 twelve 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.

Intraarticular Corticosteroid Injections Have Systemic Effects

Intraarticular corticosteroid injections are known to have systemic endocrine effects similar to epidural corticosteroid injections. Following a single intraarticular 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) intraarticular 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 the suppression with either an epidural steroid injection or an intraarticular steroid injection are virtually identical.

Systemic Corticosteroid Increases Infection Risk

Study of oral corticosteroid versus placebo with meta-analysis demonstrate an increased risk of infection within the steroid group. One study reported a relative risk (RR) of 1.6 for participants taking more than 10 mg prednisone/day or a cumulative dose greater than 700 mg [15]. A dose-dependent relationship was also observed for infection risk, which increased from a RR of 1.5 with low doses to greater than 8 with doses above 40mg/day [16]. Among patients with rheumatoid arthritis on oral prednisone, the RR of hospitalization for pneumonia ranged from 1.4 (<5 mg/day dose) to 2.3 (>10 mg/day dose) when compared to 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 a similar effect on the immune system as does 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 intraarticular 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 intraarticular corticosteroid injection versus 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 to no injection [RR=1.52 (CI = 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 suggests that, even among vaccinated individuals, an intraarticular corticosteroid injection before or during flu season may cause increased risk of infection. Whether or not 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 healthcare resources are of utmost concern, there may be times when interventional pain procedures may still be indicated [20]. The Center 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 under-treatment 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 counter-productive 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 intraarticular or epidural corticosteroid injections and COVID-19 infection rate or severity of illness.

For continuous updates and guidance from SIS refer to: <https://www.SpineIntervention.org/COVID-19> [24].

Summary

1. Epidural and intraarticular corticosteroid injections have systemic effects.
2. No study has yet been published that examines whether or not 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 intraarticular 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 a candidate 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 "non-emergent or non-essential" 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/COVID-19>.

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