CURRENT CONCEPTS REVIEW

The Effect of Intra-articular Corticosteroid Injections on Vaccine Efficacy: A Current Concepts Review

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Abstract

Orthopedic surgeons commonly perform corticosteroid injections. These injections have systemic side effects, including suppression of the hypothalamic-pituitary adrenal axis. Due to this suppression, there is a theoretical risk of corticosteroid injections affecting the efficacy of the novel COVID-19 vaccines. This potential interaction led the American Academy of Orthopedic Surgeons to recommend, "avoiding musculoskeletal corticosteroid injections for two weeks before and one week after COVID vaccine administration." This review examines the literature underlying this recommendation. An extensive literature review was performed through PubMed, MEDLINE, and Google Scholar from database inception to May 2022. Keywords searched were COVID, coronavirus, vaccine, vaccination, steroids, and corticosteroids. Search results included articles written in the English language and encompassed reviews, case series, empirical studies, and basic science articles. There is no definitive evidence that corticosteroid injections affect COVID-19 vaccine efficacy or increase the risk of contracting COVID. The authors recommend orthopedic surgeons follow the AAOS guidelines, which recommend avoiding injections two weeks before and one week following COVID vaccine administration. Additional research is needed to better define this theoretical risk, especially since there is good evidence that injections suppress the hypothalamic-pituitary-adrenal-axis.

Level of evidence: IV

Keywords: Corticosteroid, COVID, Injection, Vaccine

Introduction

Intra-articular corticosteroids are commonly injected in orthopedic surgery.[1] It is well known that intra-articular corticosteroids can have systemic side effects, namely raising blood glucose levels.[2,3] Novel mRNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are highly effective against COVID infection.[4,5] These vaccines are widely distributed, with over 550,000,000 doses dispensed.[6] Vaccine effectiveness has been shown to be decreased in immunocompromised patients (organ transplant, hematologic malignancy, chemotherapy).[7–11] Therefore, it is important that orthopedic surgeons understand the literature on the effect of corticosteroid injection on the immune system and vaccine efficacy.[12]

Materials and Methods

Immune System Overview

The immune system is broadly divided into two components: innate and adaptive. The innate immune system provides the non-specific, first-line of defense. It includes physical barriers such as skin, chemical barriers like tears and mucous, and cellular defenses. The cellular defenses are non-specific with quick onset (0-96 hours). As they are non-specific, antigens are not part of the innate immune system. The adaptive immune system, by contrast, provides a specific defense against pathogens. The hallmark cells are the T and B lymphocytes. B cells create antibodies against a specific pathogen. Cytotoxic T cells destroy marked cells, and helper T cells help regulate the system to guard against autoimmunity.[13] Vaccination

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utilizes the adaptive immune system to produce immunity [Table 1].

Vaccine Mechanism of Action

Table 1. Immune System Functions

	Innate Immune System	Adaptive Immune System
Specificity	Non-Specific	Specific
Response Time	Minutes to Hours	Days to Weeks
Memory	Absent	Present
Components	Physical Barriers (Skin) Chemical Barriers (Tears, Mucus, Saliva) Cellular Defense (Macrophages, Neutrophils, Basophils, Mast cells)	Cellular Defense (T and B Lymphocytes) Antibodies

There are three primary vaccine mechanisms of action. Live attenuated vaccines, such as the chicken pox vaccine, contain a modified version of a pathogen that has been weakened to make it less virulent. This pathogen is incorporated into the vaccine, and the relatively small dose of the virus or bacteria replicates in the body, creating an immune response.

Inactivated vaccines, such as the polio vaccine, contain an altered pathogen which cannot replicate in the patient. The body produces antigens against the altered pathogen.[14]

Both the Pfizer BioNTec and Moderna vaccines are novel mRNA vaccines. These vaccines contain a lipid nano-particle-formulated nucleoside-modified RNA which encodes for spike protein of the SARS-CoV-2 virus.[4,15] The mRNA in the virus causes the body to produce the spike protein via translation, which subsequently activates the adaptive immune system against the protein.

Table 2. Vaccine Mechanisms of Action

	Live Attenuated Vaccine	Inactivated Vaccine	mRNA Vaccine
Mechanism of Action	Weakened virus	Killed virus	RNA encoding spike protein
Advantages	Robust immune response	Safe and stable compared to live attenuated vaccines	Easy and quick to mass produce
Disadvantages	Not recommended to individuals with compromised immune system	Immune response not as effective as live attenuated	Novel vaccine type
Examples	Measles, Mumps, Rubella, Chickenpox	Polio	COVID-19

The Johnson & Johnson vaccine uses a genetically altered adenovirus which carries DNA that allows for transcription of and translation of the spike protein. Again, the adaptive immune system activates against the protein [Table 2].[16]

Common Steroids

Common steroids include hydrocortisone, methylprednisolone, dexamethasone, betamethasone, prednisolone, and triamcinolone. Dexamethasone is available in dexamethasone sodium phosphate and dexamethasone formulations while triamcinolone comes in triamcinolone acetonide and triamcinolone hexacetonide formulations.[17] A 2015 Cochrane review found no statistically significant risk of serious adverse events for patients who had intra-articular corticosteroid injections.[18] However, intra-articular injections have been linked with articular cartilage damage,[17] increased blood glucose levels,[19] and increased risk of infection when performed within 3 months of arthroplasty.[20, 21]

Hypothalamic Pituitary Adrenal Axis Overview

To understand the systemic effects of corticosteroids, we have to know the hypothalamic pituitary adrenal (HPA) axis. The hypothalamus releases corticotrophin -releasing hormone (CRH). CRH acts on the anterior pituitary gland, which releases adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal cortex, which releases cortisol. Cortisol then inhibits the hypothalamus and pituitary gland. Endogenous and exogenous steroids suppress release of CRH and ACTH, downregulating the HPA axis. The degree of suppression is related to both the dose and duration of the therapy.[22] This suppression has been shown to occur with intra-articular steroid injections[23] and can cause adrenal insufficiency or, rarely, even Cushing syndrome.[23]

The HPA axis and immune system are intertwined, as inflammatory cytokines produced by the immune system activate the HPA [Figure 1].[24-26]

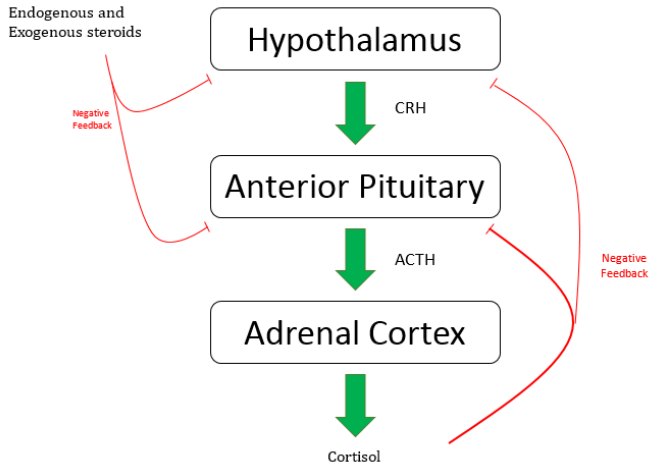

Figure 1. The Hypothalamic Pituitary Adrenal Axis. Corticotrophin-Releasing Hormone (CRH), Adrenocorticotropic Hormone (ACTH)

Peripheral Injection Effects on HPA Axis

Regan et al. conducted a narrative review on the effects of peripheral steroid injections on the HPA axis. They concluded "There is evidence of consistent transient HPA axis suppression following peripheral corticosteroid

injection. Suppression is generally reported to last for up to 2–4 weeks although some studies using higher cumulative doses report suppression lasting eight weeks or longer".[27] This was based on analysis of 12 studies.

Bird et al. conducted a double-blind randomized controlled trial (RCT) of 30 patients with rheumatoid arthritis (RA). The patients received 3 different steroid preparations into the knee. Max plasma cortisol suppression occurred 2-4 days after the injection with suppression lasting <4 weeks for triamcinolone acetonide and >4 weeks for methylprednisolone acetate and prednisolone t-butyl acetate.[28]

Armstrong et al. performed an observational study in 21 RA patients who underwent a knee injection with methylprednisolone acetate looking at plasma cortisol levels for one week. They found the plasma cortisol was maximally suppressed by 24 hours, with 64-81% decreases in plasma cortisol.[29]

Esselinckx et al. conducted an observational study with osteoarthritis (OA), reflex sympathetic dystrophy, or shoulder hand syndrome in the knee or shoulder with 40-120 mg of triamcinolone acetonide for 15 days. The study showed that a cohort of patients saw suppression of urinary free cortisol even 72 hours post-injection.[30]

Derendorf et al. conducted an observational study following 42 patients with RA who underwent knee injection with 10-40 mg triamcinolone hexacetonide, 20-40 mg triamcinolone acetonide, or 5.7 mg betamethasone following serum cortisol for three weeks. Suppression was seen for one week which was dose dependent.[31]

Lazarevic et al. conducted an observational study of 21 patients with RA, OA, or psoriatic arthritis (PA) who had intra-articular or intramuscular injections with 40 mg methylprednisolone acetate. They followed serum cortisol for 72 hours. The maximal suppression averaged 21.5% after 24 hours with 4/21 patients having continued suppression at 72 hours.[32]

Furtado et al. performed an RCT of intra-articular versus intramuscular 20-40 mg triamcinolone hexacetonide in 69 patients with RA injecting into the elbow, wrist, knee, ankle, or metacarpal phalangeal joint. They followed serum ACTH for 24 weeks and found no statistically significant levels of suppression between the two cohorts.[33]

Mader et al. conducted an observational study of 25 patients with OA, RA, PA, or pseudogout. Injections were performed into the shoulder, knee, elbow, subtalar joint, CMC joint, PIP joint, and wrist with methylprednisolone acetate at doses of 10-20 mg (small), 40-60 mg (medium), or 80 mg (large) doses. They looked at serum cortisol and 1ug ACTH stim levels with 4 weeks follow up. 12% of patients had adrenal insufficiency after one week with 8% having continued suppression after two weeks, with insufficiency correlating with larger doses.[34]

Weitof et al. performed an RCT of 24 patients with RA who received 20 mg triamcinolone acetonide injections intra-articularly into the knee and were randomized between bedrest and normal activity. They had two weeks follow up looking at serum cortisol and serum ACTH. Maximum suppression occurred after 24 hours with some individuals experiencing suppression for two weeks.[35]

Duclos et al. conducted an observational study of 10 patients with prior trauma to the knee, ankle, or wrist who received betamethasone or cortivazol 1.87-7 mg. They followed plasma cortisol and 1ug ACTH stim test for two weeks. 90% of patients had adrenal insufficiency after 48 hours with 20% still suppressed at 1 week. 0% were suppressed at two weeks.[36]

Habib et al. performed a case control study of 40 patients with knee OA being injected with 6mg of betamethasone. They followed serum cortisol and 1ug ACTH stim test with eight weeks follow up. Their cohort was significant for one patient with continued suppression three weeks after injection.[37]

Habib, Jabbour et al. followed up the aforementioned study with an RCT comparing intra-articular methylprednisolone acetate (80 mg) versus sodium hyaluronate (60mg) in 40 patients with knee OA. They had 8 weeks follow up of serum cortisol and 1ug ACTH stim test. 25% of patients had adrenal insufficiency after 2-4 weeks with all participants returning to normal function after 8 weeks.[38]

Habib, Khazin et al. then conducted a case control study of 40 patients with knee OA. They received 160 mg methylprednisolone. Serum cortisol and 1ug ACTH stim test were followed for 8 weeks. 40% of patients were noted to have adrenal insufficiency >1 week, 35% > 4 weeks, 20% >6 weeks, 10% >8 weeks.[39]

Steroid and Vaccine Efficacy

It is well established that corticosteroid injections affect the HPA axis.[2, 3, 28–37] several studies have taken this a step further, looking at whether this suppression affects vaccine effectiveness.

Systma et al. performed the only study to directly evaluate the effect of intra-articular steroid injections and vaccine effectiveness. The retrospective study included 15,068 joint steroid injections in 4,804 patients who received the influenza vaccine. The patients who received the injection and vaccine were compared to a control group who only received the vaccine (n = 43,236). The steroids received by patients who developed influenza were methylprednisolone (78.9%), betamethasone (10.9%), and triamcinolone (10.1%). The mean dose was equivalent to 659 mg of methylprednisolone. The influenza rate was 1.08% in the control group compared to 1.64% in the injection group, giving a relative risk of 1.52. However, the study did not look at the timing of steroid injection relative to vaccination, making the exact causal effect difficult to determine.[40]

There are also studies that examine the effects of inhaled or systemic steroids on vaccine efficacy.[41-44]

Three studies looked at steroid administration affecting influenza vaccine efficacy, and found no difference in post-vaccination titers.[41,42] Deroux et al. compared COPD patients taking systemic steroids (n = 33), inhaled steroids (n = 87), and control without steroid use (n = 42). No significant difference in titer levels was observed 4 and 24 weeks after vaccination.[41] Inoue et al. compared COPD patients on oral

steroids (n = 11), inhaled steroids (n = 17), and controls without steroid use (n = 20). Again, there were no significant differences in titers 4-6 weeks after vaccination.[42] However, Hanania et al. performed a substudy on a multicenter, randomized, double-blinded, controlled crossover study on the influenza vaccine in patients with asthma. They compared 294 patients who received either placebo (n=139) or influenza vaccine (n=155). They observed patients who were taking medium-dose inhaled steroids, high-dose inhaled steroids, or oral steroids. A single antigen (influenza B antigen) was decreased only in the high-dose inhaled steroid group.[45]

Two additional studies examined steroid administration and pneumococcal vaccine titer levels.[43, 44] Lanhood et al. examined patients with asthma on every day or every other day steroids (n = 14) compared with patient receiving no steroids (n = 14). They found no significant difference in titers four weeks post-vaccination.[44] Steentoft et al. examined patients with COPD taking steroids before vaccine (n = 15), starting steroids after vaccine (n = 13), on continuous steroids before and after vaccination (n = 9), and control group on continuous steroids not given vaccine (n = 12). They examined titers four- and six-months post-vaccination. Antibodies were lowest in patients taking steroids before vaccination. Post-vaccine steroid patients had 2x increases in titers, while continuous steroid patients had 1.5x increase. There was no increase in patients who did not get vaccinated.[43]

Steroids and Risk of Contracting COVID

A narrative review examining the association between corticosteroid injections and COVID infection found that "There is currently no evidence that these physiological changes translate into a clinically meaningful increased risk of COVID-19 infection or related morbidity or mortality, but there is also no persuasive evidence that they do not".[27] This statement was based on two studies looking at injections and COVID infection risk.

The larger study was a retrospective review of 443 patients undergoing 504 total intra-articular injections at the NHS trust in the UK from 2/1/2020 to 6/30/2020. There were 461 and 43 spinal injections. The authors reviewed the electronic medical record and found that no patients tested positive for COVID. Only 11 had been tested. However, two patients were found to have IgG antibodies, consistent with prior infection. Notably, both patients were asymptomatic. Based on this retrospective review, the authors concluded that the risk of contracting COVID after steroid injection was low. Notably, the authors did not perform injection in patients who were deemed high risk for COVID.[46]

A second study was conducted on 71 patients, with 66 making it to final follow up. Patients received image-guided corticosteroid injections at one of two centers in Massachusetts between 4/15/2020 and 5/22/2020. 43 patients received peripheral injections while 28 underwent spinal injections. The patients were followed for 1 month by looking at their electronic medical record and making a phone call. The cohort yielded one positive test, leading to an incidence of 1.52%. This was not statistically higher than the community incidence of 0.91% at that time. However, the study may have been insufficiently powered to detect a true difference.

Society Recommendations

The most relevant recommendation for orthopedic surgeons is from the American Academy of Orthopedic Surgeons (AAOS). Their official guidelines state "The AAOS Patient Safety Committee recommends avoiding musculoskeletal corticosteroid injections for two weeks before and one week after COVID vaccine administration".[47]

However, it is also important for orthopedic surgeons to be aware of societal recommendations from general medical organizations as well as other specialties that perform corticosteroid injections.

The Center for Disease Control (CDC) does not provide any specific guidelines for timing of intra-articular steroid injections for either the COVID-19 vaccine[48] or vaccines in general.[49]

The Spine Intervention Society and American Society of Interventional Pain Physicians recommend that physicians consider vaccination and steroid injection timing. The Spine Intervention Society states "physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible".[50] Similarly, the American Society of Interventional Pain Physicians recommend against injection of short acting steroids two weeks before vaccination and long-acting steroids four weeks before vaccination. They also recommending attempting to delay procedures until two weeks post-vaccination.[51] In contrast, the American Society of Pain and Neuroscience's guidelines state "There is no evidence that patients receiving epidural steroid therapy for the management of pain are at increased risk of adverse outcomes from COVID-19 vaccination." Therefore, their recommendation is that "Neuraxial steroid injections do not need to be deferred when indicated in the context of COVID - 19 vaccination".[52]

Conclusion

There is no definitive evidence that corticosteroid injections affect COVID-19 vaccine efficacy or increase the risk of contracting COVID. However, further research is needed to better define this risk, especially since injections suppress the HPA-axis. Physicians can share the current evidence with their patients in order to engage in maximally effective shared decision making. While research on this subject continues to evolve, the authors recommend orthopedic surgeons follow the AAOS guidelines, which recommend avoiding injections two weeks before and one week following COVID vaccine administration.

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