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REVIEW

The COVID-19 vaccine and interventional procedures: Exploring the relationship between steroid administration and subsequent vaccine efficacy

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Abstract

Objective: Collate available evidence and provide guidance on whether to delay steroid injections after receiving a vaccine, and whether to delay vaccination if a recent steroid injection has been administered, leaving formal recommendations to various national societies.

Methods: A literature search was performed to identify information pertinent to steroid administration and the subsequent downstream effects on vaccine efficacy. The search was initiated on December 20, 2020, and the terms used were (steroid OR cortisone OR dexamethasone) AND (vaccine). The studies were limited to articles in the English language.

Results: Six studies specifically addressed the effect of steroids on vaccine efficacy. Three of the 6 studies indicated that steroids could be used during the peri-vaccine period without significant suppression of the immune response. One study associated intra-articular steroid injections with an increased risk of developing influenza even when vaccinated. The remaining 2 studies had mixed findings. One study showed that patients who received dexamethasone, but not prednisolone were able to mount an immune response resulting in increased IgG. Another study showed that vaccine efficacy was maintained if patients were on continuous steroids or steroids after vaccination, but not if they stopped steroids prior to vaccination.

Conclusions: Although there is no shared consensus in the studies reviewed, all but one study noted scenarios in which patients receiving steroids can still be successfully vaccinated.

KEYWORDS
coronavirus disease 2019, efficacy, pain, steroids, vaccines

INTRODUCTION

Steroid injections are widely used in clinical practice for the treatment of chronic pain, but there are little clinical data on how they affect vaccine efficacy. As more patients are being inoculated with the coronavirus disease 2019 (COVID-19) vaccine, this question is becoming more important. The only published recommendations around this specific question are from the Spine Intervention Society Fact Finder published in February 2021, which recommends withholding steroid injections no less than 2 weeks prior to the COVID-19 vaccine and no less than 1 week following the vaccine. The American Society of Pain and Neuroscience published a review and concluded that there is no evidence that steroid injections affect COVID vaccine efficacy. This paper delves deeper into the available evidence from clinical studies. The ideal way to answer this question is to examine the pharmacokinetics of steroids in the body and their pharmacodynamic effects on the immune system, and to compare these with the onset and peak effect of the vaccines themselves. However, there are sparse data to conclusively answer the first question and the vaccine is too new to definitively answer the second.

Vaccines can be whole virus, subunit, nucleic acid, toxoid, or viral vector based. The goal of a vaccine is to induce the production of antibodies to those pathogens. This allows rapid clearance of the pathogens in the future upon repeat exposure. This process is mediated by B cells that produce the antibodies and T cells that effect the cellular response, and depends on the ability of the body to produce antibodies to the appropriate antigens. In the case of the COVID-19 mRNA vaccines, 2 separate injections are required to achieve this antibody response. Specifically, the spike (S) protein is the key element of cell binding and subsequent viral entry into the cell. The BioNTech vaccine is a lipid nanoparticle-formulated nucleoside-modified RNA that encodes for the spike protein of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus.[1] It has been shown that two 30-μg doses of BNT162b2 elicit high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type $CD4^+$ T-cell responses. S-specific $CD8^+$ and T helper type 1 (T_H1) $CD4^+$ T cells also expand, with a high fraction producing interferon-γ (IFNγ).[2]

It should be noted that the aforementioned COVID-19 vaccines are unique in that they are mRNA based. For example, the annual influenza vaccine is either live attenuated (modified pathogen) or inactivated (pathogen particles). Thus, any interpretation of the data from currently available studies should be appraised with that caveat in mind.[3] One commonality for all vaccines, however, is the need for a robust immune response to confer immunity.

The Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP) published expert consensus guidelines for the safety of vaccinations in patients with altered immunity.[4] Inactivated vaccines can be safely administered, including killed whole-organism, recombinant, subunit, split-virus, toxoid, polysaccharide, or protein-conjugate vaccine. However, interventional pain societies have generally been silent on the ideal timing of vaccination before or after a steroid injection, given a relative lack of high-quality evidence. This lacuna has grown during the COVID pandemic, with mass immunizations against COVID becoming a priority for the government. Through this narrative review, we have attempted to collate the available evidence regarding the efficacy and safety of vaccines in patients undergoing steroid treatment via any route, with a special note of guidance from the Spine Intervention Society (SIS) regarding the timing of the COVID vaccine with interventional procedures.[5]

Key Practice Points

- The purpose of this manuscript was to review the current literature on the relationship between steroid administration and subsequent vaccine efficacy.
- The data was analyzed and collated. The authors then attempted to determine if recommendations could be made for patients receiving an interventional procedure with steroids before or after vaccine administration.

Highlights

- The advent of COVID-19 vaccines brings into question their efficacy in the setting of procedural steroid administration.
- Based on current available data it is reasonable to delay procedures involving steroids for 1-2 weeks following vaccine administration.
- In addition, it is also reasonable to delay vaccinations for approximately 2 weeks after a procedure involving steroids.

METHODS

A literature search was performed using Ovid-Medline and Embase, Cochrane Central, PubMed, and Google Scholar in an effort to identify any information that was pertinent to steroid administration and the subsequent downstream effects on vaccine efficacy. The search terms used were (steroid OR cortisone OR dexamethasone) AND (vaccine OR vaccination). On December 20, 2020, a search was performed that yielded 3960 articles. The studies were limited to articles in the English language. Eligibility criteria included studies where patients were greater than 18 years of age and where patients received

vaccinations while concomitantly receiving steroids via any route. Exclusion criteria included studies where patients were being treated with steroids in addition to other immunosuppressive agents, animal studies, pediatric studies, case reports, and expert opinion. These articles were then screened by the reviewers based on applicable titles and abstracts. Of these articles, 6 were deemed appropriate.

The gathering of relevant data involved identifying scenarios in which adult patients were exposed to steroids while concurrently being administered a vaccine. The aim was to analyze the available data and determine any relationship that exists.

RESULTS

A total of 6 articles were found with our predetermined selection criteria. The largest study was conducted by Sytsma et al. in the form of a retrospective review of 15,068 major joint steroid injections. Of these injections, 4804 patients were vaccinated (cases). When these patients were compared with vaccinated controls (patients who received the vaccine and no joint steroid injection; $n = 43{,}236$) the investigators found that vaccinated patients receiving a major joint injection were at increased risk for developing influenza when compared with vaccinated control patients.[6] The relative risk was 1.52, but the influenza rates were low in both groups (1.08% for the control group and 1.64% in the vaccinated group that had steroid injections). The average steroid dose was equivalent to 659 mg of methylprednisolone. The authors concluded that the risk for influenza is higher in patients getting intra-articular steroid injections during influenza season, even in vaccinated patients. The retrospective nature of the study precludes analysis of the timing of steroid administration relative to the timing of vaccination, making it difficult to establish a temporal association between the two and the higher risk of contracting influenza.

Other groups studied the effect of systemic immunosuppressive agents on vaccination response (Table 1). Even though the administration route and frequency are not reflective of a single time steroid administration in the joint space or epidural space, steroids injected in the joint or epidural space may get absorbed into the systemic circulation, albeit over a period of several days to weeks. These studies can therefore serve as a guide to determine potential effects of steroid injections on vaccination outcomes. Table 1 lists the relevant studies evaluating vaccine efficacy after systemic steroid administration.[7–11]

Summarizing the available evidence concerning steroid usage and subsequent vaccine efficacy, most studies except the retrospective review have small numbers. Three of the 6 studies showed that there was no difference between the steroid administration groups and control groups in terms of antibody titers after vaccination. One study associated intra-articular steroid injections with an increased risk of developing influenza even when vaccinated, indicating that intra-articular steroid injections may reduce vaccine efficacy. The remaining 2 studies had mixed findings. Naito et al. showed that patients taking dexamethasone, but not prednisolone, had an increase in IgG after vaccination. Steentoft et al.[11] showed that patients on continuous steroids and those that started steroids after vaccination had a significant increase in antibody titers. Patients who stopped steroids prior to vaccination were noted to have the least significant rise in antibody titers. The authors noted that all the subjects had pneumococcal disease in the past, which may have conferred pre-existing immunity and thus confounded the results.

DISCUSSION

To address whether or not procedural steroids have an effect on vaccine efficacy, the first question to answer would be whether or not procedural steroids result in significant systemic uptake. The synthetic steroids that are typically injected into the epidural and joint spaces are lipophilic and have a higher glucocorticoid receptor binding affinity when compared with endogenous steroids and are therefore more potent.[12] The systemic effects of oral steroids are well described, especially during long-term administration. When looking at injected steroids, there is a paucity of data on their specific impact on immune function. However, we do have indirect evidence that steroid injections result in some degree of systemic uptake with a potential impact on normal endocrine function.

At this time, several studies have demonstrated systemic effects of local steroids injected in joints and the epidural space, especially with particulate steroids (Appendix 1). Injection of particulate steroids in the epidural and intra-articular space have been shown to be associated with serum cortisol reduction, that can last from 2 to 3 weeks.[13,14] Abdul et al.[15] showed that a single epidural injection of 80 mg methylprednisolone reduces ACTH levels, lasting for 14 days with a nadir at 7 days, and a return to baseline by day 28. Friedly et al. showed that epidural triamcinolone leads to the greatest decrease in cortisol at 3 weeks, followed by methylprednisolone. Betamethasone and dexamethasone had the least decreases in cortisol levels at 3 weeks.[16] Clinical manifestations from the cortisol suppression, however, are usually mild and self-limited. In a study by Kang et al.,[17] studying the systemic effects of epidurally injected dexamethasone, facial flushing was the most common side effect and only 0.4% patients reported elevated blood sugar. These authors also showed that the systemic effects were site dependent, being higher in the cervical than lumbar injections.

The preponderance of evidence therefore hints at systemic uptake and effects lasting up to 3–4 weeks after

TABLE 1 Studies evaluating the effect of systemic steroids on subsequent vaccine efficacy

Manuscript title	Authors	Groups studied	Results
Joint corticosteroid injection associated with increased influenza risk	Sytsma et al. (2018)[6]	Cases: Patients who received intra-articular steroid injections in addition to the flu vaccine (n = 4804) Controls: Patients who did not receive intraarticular steroid injections, but received the flu vaccine (n = 43,236)	Vaccinated cases (patients who received intra-articular steroid injection and flu vaccine) were at increased risk of subsequent influenza development when compared to controls (RR = 1.52; 95% confidence interval 1.20–1.93)
Influence of corticosteroid therapy on the serum antibody response to influenza vaccine in elderly patients with chronic pulmonary diseases	Inoue et al. (2013)[7]	Three arm prospective study of patients with COPD receiving influenza vaccine; Patients on oral corticosteroid therapy (median prednisolone-equivalent dose 10 mg/day; 2.5–25 mg/day) (n = 11) Patients on inhaled corticosteroid therapy (median budesonide-equivalent dose 800 mcg/day; 400–1600 mcg/day) (n = 17) Patients not on corticosteroid therapy (n = 20)	No statistically significant difference in antibody titers increase (baseline versus 4–6 weeks post-vaccination) among 3 groups
Dexamethasone did not suppress immune boosting by personalized peptide vaccination for patients with advanced prostate cancer	Naito et al. (2008)[8]	Patients receiving prednisolone (10 mg/day) followed by dexamethasone (1 mg/day) (n = 6) Patients receiving only prednisolone (n = 1) Patients receiving only dexamethasone (n = 4)	IgG levels were not significantly increased in the prednisolone group IgG levels increased in the dexamethasone group
Response to pneumococcal vaccine in patients with chronic obstructive lung disease—The effect of ongoing, systemic steroid treatment	Steentoft et al. (2006)[9]	Patients taking steroids before vaccination (n = 15) Patients started on steroids after vaccination (n = 13) Patients on continuous steroids before and after vaccination (n = 9) Control group on continuous steroids (on continuous steroids) not being administered the vaccine (n = 12)	Patients taking steroids before vaccination had the least significant rise in antibody titers at 4 weeks and 6 months Patients vaccinated and then treated with steroids showed a significant rise in antibody titers (×2 baseline) when compared to their non-vaccinated control counterparts on continuous steroids at 4 weeks and 6 months ($p < 0.05$) Patients who had continuous steroid treatment had titers that were 1.5 times their baseline at 4 weeks and 6 months No increase in antibody titers were reported in the non-vaccinated control group (i.e., no antibody response) at 4 weeks and 6 months All results were reported at 4 weeks and 6 months

(Continues)

TABLE 1 (Continued)

Manuscript title	Authors	Groups studied	Results
Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly patients with COPD	Deroux et al. (2005)[10]	Patients taking systemic steroids, >10 mg of prednisolone daily or equivalent dose of another steroid (n = 33) Patients taking inhaled steroids, any dose (n = 87) Control group not being treated with steroids (n = 42)	All groups showed increased titers (A/H1N1, AH3N, and B) at 4 weeks with no significant difference between groups The titers for influenza B were sustained at 24 weeks with no significant difference between groups Antibodies were measured at 4 weeks and 24 weeks
Antibody levels and response to pneumococcal vaccine in steroid-dependent asthma	Lahood et al. (1993)[11]	Patients with steroid-dependent asthma receiving prednisone daily or alternating daily (10–35 mg) (n = 14) Patients with asthmareceiving no steroids daily (n = 14)	No statistically significant difference in mean pneumococcal antibody titer between steroid and control groups at 4 weeks post vaccine

Abbreviations: COPD, chronic obstructive pulmonary disease; RR, relative risk.

epidural and joint steroid injections. Steroids injected into joints or perineural tissue, hence, can be taken up in the systemic circulation via diffusion and potentially alter the immune response to vaccinations, rendering them less effective.

Glucocorticoids are known to have profound effects on the immune system, particularly with systemic administration over extended periods. Low steroid doses are described as less than 20 mg/day, moderate as 40 mg/day, and high as greater than 40 mg/day. These are based on general consensus, with no specific guidelines to recommend specific cutoffs. Even at pulse intervals, steroids affect leukocyte aggregation and circulation.[18]

The effects of steroids on the immune system begin at the molecular level. Glucocorticoids diffuse passively across cell membranes and bind intracellular glucocorticoid receptors, which then translocate into the nucleus, resulting in multiple downstream effects that can impact the immune system.[19] Although glucocorticoids impair neutrophil migration, which leads to neutrophilia, they do not affect the phagocytic response. These effects do not carry over to the circulating levels of B cells in the acute setting, but with prolonged administration, the number of B cells may be reduced. IgG and IgA levels may decrease by 10–20 percent in the first few weeks of treatment with regular moderate-to-high dose (≥40 mg per day) steroid administration.

In low-to-moderate doses, glucocorticoids have variable effects on T lymphocytes. At low doses, the effects are primarily on naive CD4 T cells rather than effector and memory T cells.[20] To the best of our knowledge, steroids reduce Th1 and Th2 derived cytokines in activated T cells.[21] Because the COVID vaccine helps proliferate the antigen specific Th1-type $CD4^+$ T-cell responses, there can be a theoretical link between steroid administration and reduced efficacy of vaccination.

Due to the potential for steroids to affect the immune system, the question of efficacy and safety of immunizations in patients with a potentially altered immune response, such as those undergoing steroid injections for chronic pain, has often been discussed. The largest available study specifically addressing the question of whether steroid injections could render subsequent vaccinations ineffective comes from a large retrospective study of 15,068 patients who underwent major joint steroid injections. The results indicated that steroid injection patients were at significantly higher risk of influenza compared with control patients who did not receive a steroid injection.[6] Although there is a paucity of data on the specific effects of epidural or intra-articular steroid injections on vaccine response, the above notion of major joint steroid injections increasing the risk of a vaccine being inefficacious has been extrapolated to other interventions for chronic pain, leading to a variability in practice among interventional pain clinics.

The ACIP suggests that patients on prednisone doses greater than 20 mg/day for more than 14 days may have suppressed immune responses.[8] They suggest stopping steroid therapy when administering killed or attenuated vaccines. Live vaccines may be given to patients on steroid for less than 14 days, and with low doses of less than 20 mg/day of prednisone or equivalent steroid. Most critically for the interventional pain specialists, there are no contraindications when the steroid is given as an intra-articular, bursal, or tendon injection. There are no consensus recommendations or data on the use of epidural steroid injections.

With the onslaught of COVID-19 in the United States in the early part of 2020, most elective procedures, including steroid injections for chronic pain, had to be postponed. Recommendations following an expert pain management panel by Cohen and colleagues on best practices for pain management advocate for a

tailored pain management approach for each patient based on patient and health-system-specific factors (risk-benefit calculation for having telemedicine versus in-person pain procedure, probability of benefit, and probability of risk to the provider).[22] However, the Centers for Medicare and Medicaid Services (CMS) now recommends a tiered care system based on acuity and nature of visit. Because many pain procedures, if delayed, would result in patient harm, pain, or suffering, such procedures for analgesia would fall under Tier 3 and in-person evaluation and treatment should not be postponed.[23] They do not, however, make specific recommendations with regard to these procedures and COVID vaccination given relatively little published data at the current time.

CONCLUSION

There is not enough literature to guide definitive recommendations concerning the timing of steroid injections relative to vaccinations and vice versa. Injected steroids can have systemic effects as they are slowly cleared from the site of injection over a period of several days to weeks. However, even after systemic administration of steroids, vaccines seem to be efficacious in stimulating an immune response. There is therefore no strong evidence to suggest delaying vaccination before or after a steroid injection. However, given that the Pfizer and Moderna vaccines in the United States are novel mRNA-based immunizations, and there is no literature to evaluate antibody response to these vaccines after injected or systemic steroids, this conclusion should be interpreted within the context of this limitation. With the risk of severe infection and high mortality associated with COVID-19, and the stakes of an adequate immune response to vaccination being high, practices may have to use an individualized approach to proceeding with steroid injections. In the absence of large prospective studies on the immune response to COVID vaccines after steroid injections, it is reasonable to delay procedures involving steroids for approximately 1 to 2 weeks after vaccine administration, and to delay vaccinations for approximately 2 weeks after a procedure involving steroids.

There are additional considerations when a patient is taking moderate to high dose steroids for more than 2 weeks. The ACIP recommends deferring live vaccinations for at least 4 weeks after discontinuation of systemically absorbed steroids.[8] This allows the patient's body to recover from the immunosuppressive effects of the steroids. Without additional studies, we can only infer that a similar time period of 4 weeks after steroid cessation may be needed prior to administration of the COVID-19 vaccine.

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CONFLICTS OF INTERESTS

None of the above authors have any conflicts of interest to disclose.

DATA ACCESSIBILITY

The data required to reproduce the above findings are available to download from each respective publishers.

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APPENDIX 1

SYSTEMIC EFFECTS OF LOCALLY INJECTED STEROIDS IN JOINTS AND EPIDURAL SPACE

Manuscript title	Authors	Study	Results
Systemic effects of fluoroscopically guided epidural steroid injection with dexamethasone	Kang et al. (2019)[17]	A retrospective review of the systemic effects after a single dexamethasone injection at the cervical or lumbosacral levels	Facial flushing was the most common systemic effect, with only 0.4% reporting elevated blood sugar and 0.5% reporting systemic edema. The systematic effects were higher in patients receiving cervical injections than lumbar ones, likely because the size of the dorsal venous plexus is larger at the cervical level
Systemic effects of epidural steroid injections for spinal stenosis	Friedly et al. (2018)[16]	A multicenter randomized controlled trial that described the effect of either a single epidural steroid injection or local anesthetic only epidural injection on cortisol levels in 400 patients with spinal stenosis	Twenty percent of patients in the steroid group had cortisol reductions at 3 weeks, compared to 6.7% of patients in the lidocaine only group. The use of insoluble steroids, such as methylprednisolone or triamcinolone, had an average of a 3-week cortisol reduction of 41% from baseline. Those injected with betamethasone or dexamethasone did not have significant reductions in cortisol levels compared to the lidocaine injection group.
Hypothalamic pituitary adrenocortical axis suppression following a single epidural injection of methylprednisolone acetate	Abdul et al. (2017)[15]	Prospective study	A single epidural injection of 80 mg methylprednisolone reduces ACTH levels, with a nadir at 7 days but lasting until 14 days, returning to normal by day 28
IA glucocorticoid injections and their effect on HPA-axis function	Johnston et al. (2015)[14]	Review	A single IA steroid injection can cause a sharp decline in cortisol levels, and the subsequent HPA axis suppression can last up to 4 weeks. The steroid itself can be retained in the joint for 2–3 weeks, but screening urine can show the presence of synthetic glucocorticoids up to 9 months after a single IA injection. TA and TH in particular have the lowest solubility profiles, followed by prednisolone and then hydrocortisone. TA and TH have peak levels 8 h after IA injections and are completely cleared from the injection site by 3 weeks. Methylprednisolone has peak levels between 2 and 12 h and complete clearance after 5 days.
Diagnosing the unrecognized systemic absorption of IA and epidural steroid injections	Lansang et al. (2009)[13]	Case series of 3 patients misdiagnosed with endocrine disorders	The patients developed iatrogenic Cushing syndrome after receiving epidural or joint injections with 40–60 mg of triamcinolone at a time
Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects	Kay et al. (1994)[24]	Prospective study that measured cortisol and ACTH levels in 14 patients receiving 3 non-image-guided epidural steroid injections of 80 mg triamcinolone at weekly intervals	Both cortisol and ACTH levels were reduced at one month after the last epidural steroid injection

Abbreviations: HPA, hypothalamic-pituitary-adrenal; IA, intra-articular; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide.