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A New Consideration for Corticosteroid Injections: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/ COVID-19) Vaccination

Ian Powelson, MD,* Robert A. Kaufmann, MD,† Natasha M. Chida, MD, MSPH,‡ Jaimie T. Shores, MD*

Corticosteroid injection (CSI) is a commonly used tool in hand surgery that is often given little consideration as a potential detriment to vaccination efficacy. The authors reviewed guidelines issued by relevant societies for the timing of CSI around the severe acute respiratory syndrome coronavirus 2 vaccination period and the evidence used to support them. Ultimately, providers and patients should be adequately educated on the theoretical risks and benefits before proceeding with CSI immediately before, during, or immediately after coronavirus disease 2019 vaccination. *(J Hand Surg Am. 2022;47(1):79–83. Copyright © 2022 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Corticosteroid, corticosteroid injection, COVID, COVID-19, SARS-CoV-2, vaccination, vaccine.

HIGHLY EFFECTIVE VACCINES for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are now available to the general public.[1,2] However, recent data have demonstrated decreased vaccine efficacy among immunocompromised populations, such as those who have undergone solid organ transplants, those with hematologic malignancies, and those undergoing chemotherapy.[3–7] This raises the concern that the immunosuppressive effects of corticosteroids (CS) might also result in decreased coronavirus disease 2019 (COVID-19) vaccine efficacy, although no study has been published on this topic yet.

Corticosteroid injections (CSIs) are commonly used in hand surgery, spine surgery, rheumatology, physiatry, and pain medicine, with the specific choice of steroid and dose varying depending on indication and provider preference. Because of the absence of specific data, our colleagues in other specialties have been drawing on the existing data regarding the effect of CSIs on non-COVID vaccine efficacy in order to make recommendations about CSIs when given in the perivaccination period. Hand surgeons may be less cognizant of these recommendations because position statements regarding CSIs and COVID vaccination have not been publicly shared by the American Academy of Orthopaedic Surgeons, American Society of Plastic Surgeons, American Society for Surgery of the Hand, and American Association for Hand Surgery.

EVIDENCE OF THE SYSTEMIC EFFECT OF CSIS

Although hand surgeons commonly consider CSIs to be a localized dose of medication with a small amount of overall systemic absorption, the effects of this systemic response are measurable. The potential

*From the *Department of Plastic & Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, MD; the †Department of Orthopedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA; and the ‡Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD.*

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Corresponding author: Jaimie T. Shores, MD, 4940 Eastern Ave, Suite A513, Baltimore, MD 21224; e-mail: jshores3@jhmi.edu.

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effect of intra-articular and epidural steroid injections on blood glucose level in patients with diabetes has been the subject of numerous studies. Small cohort studies tracking the blood glucose levels after the injection of various steroids (triamcinolone, betamethasone, and methylprednisolone) at various sites (tendon sheath, carpal tunnel, intra-articular, and epidural) have demonstrated wide agreement that there is a definite increase in the blood glucose levels following injection, and the effects disappear after 2−5 days.[7−14]

Studies of epidural CSI may also be relevant. Epidural CSI and systemic glucocorticoid levels in the weeks following injection were studied to assess the possible systemic effects.[15] In a randomized, double-blinded, placebo-controlled, multicenter trial, the morning serum cortisol levels were measured at baseline and 3 weeks after injection in 400 patients with spinal stenosis aged 50 years or greater. The subjects received either lidocaine alone (placebo) or lidocaine with betamethasone (6−12 mg), dexamethasone (8−10 mg), methylprednisolone (60−120 mg), or triamcinolone (60−120 mg). There was an average 14.4% reduction in the serum cortisol level at week 3 for those who received a CSI compared with that at the baseline, whereas those who received lidocaine alone had an 8.2% increase in the serum cortisol level. Approximately 20% of the patients experienced a 50% or larger reduction in the serum cortisol level after CSI at 3 weeks, and 3.2% of the patients who received a CSI had near-complete cortisol suppression (90% or greater suppression at the baseline) at 3 weeks. This study demonstrated that a subset of patients is more sensitive to systemic steroid effect after relatively large doses of epidural steroid injections (twice or more than those typically given for hand surgery indications). The authors were unable to predict who would develop hypersensitivity to CSI but were able to demonstrate that certain steroids cause more systemic effect than others at 3 weeks. The betamethasone and methylprednisolone injection values did not differ significantly from the lidocaine-only (placebo) injection values at 3 weeks compared with that at baseline, whereas the triamcinolone and dexamethasone were significantly more likely to result in cortisol suppression at that time point (41.0% and 41.6%, respectively).

EVIDENCE OF THE INFLUENCE OF STEROIDS ON VACCINATION EFFICACY

Currently no direct data exist of which the authors are aware to address the efficacy of COVID-19 vaccination in the setting of CSI. The most common vaccination studied with steroids has been influenza vaccination. In a retrospective influenza study at Mayo Clinic, patients treated over 5 years during the influenza season who received large joint injections with CSI with or without flu vaccinations were compared with another "control" population of patients who received only flu vaccination.[16] The relative risk of developing influenza was statistically significant at 1.52 times higher in those who received the large dose of joint CSI than in those who did not. However, the overall percentage of patients who developed influenza, based on the clinical diagnosis in their medical record, was low overall in both the groups: 1.08% for the control group (vaccinated but no CSI) and 1.64% for the group vaccinated with joint CSI (vaccinated + CSI), and the percentage of patients without vaccination who developed influenza was 1.70% (CSI without vaccination). It is unknown how many patients in the unvaccinated group were vaccinated outside of the medical system or how many in the non-CSI group had received a CSI elsewhere. Of note, those confirmed to have influenza who received a CSI had received methylprednisolone (78.9%), betamethasone (10.9%), and triamcinolone (10.1%).

Data on the effect of systemic CS use have been more commonly reported. To evaluate the effect of systemic steroid use on influenza vaccine efficacy, elderly patients with chronic obstructive pulmonary disease receiving the vaccine were divided into 3 groups based on their chronic obstructive pulmonary disease management (no CS, oral CS, and inhaled CS) and compared for antibody responses to the influenza vaccination prospectively.[17] Although the total number of patients enrolled was low (48) and there was no randomization or blinding, the authors demonstrated sufficient antibody titers after the administration of the vaccine (compared with pre-administration vaccine baseline) in all 3 groups. Despite the fact that patients on chronic steroids had a lower baseline antibody titer prior to vaccination, they still mounted an appropriate response.

In a separate study, 39 patients with lung disease who received a trivalent influenza vaccine were prospectively analyzed and compared based on the use of systemic CS in subjects with a mean age of $\geq$60 years. This study demonstrated no significant difference in antibody response between the 2 groups (84% of the CS recipients demonstrated a 4-fold or greater rise in antibody level after vaccination compared with 79% of the non-CS recipients).[18] The steroid doses varied from the daily equivalent of

2.5−60 mg of prednisone, with no correlation with antibody response.

In a larger multicenter, randomized, placebo-controlled study of children and adults with asthma, trivalent influenza vaccination with systemic CS use was evaluated, and the subjects were separated into groups based on a low or no CS dose (group 1) and a moderate-to-high CS dose (group 2).[19] Primary study endpoints demonstrated an adequate immune response (>4-fold rise in baseline antibody), which was similar in both groups that received vaccination for influenza (A and B), and chronic systemic CS use did not diminish this effect. However, the authors did comment that a *post hoc* analysis demonstrated a blunting of the immune response to influenza B in the high-dose CS group.

In a review in the *Lancet Infectious Disease*, the results of 9 studies of influenza vaccination in adult patients with rheumatic diseases were examined, and an impaired immune response to vaccination was found in 4 studies, whereas no difference was found in 5 studies, although the studies that showed no difference had limited power to detect small differences.[20] The authors noted that no conclusion could be drawn about the precise effect of CS because the study populations were often on other immune-modulating drugs in addition to CS.

Vaccination safety and efficacy have also been demonstrated for yellow fever (live attenuated) and Zoster (live) in patients taking systemic CS.[21,22]

SOCIETY RECOMMENDATIONS

Several societies in the United States and Europe have made CSI recommendations for the COVID-19 pandemic in general and now, more specifically, for the perivaccination period. The American Society for Interventional Pain Physicians and the Spine Intervention Society are 2 organizations, which use CSIs with overlapping scope, that have issued guidance. The Spine Intervention Society guidance states the following[23]:

> *"…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."*

The American Society for Interventional Pain Physicians made similar recommendations in an unfinalized draft document on their website, and these have been truncated here because of space considerations[24]:

Before vaccination

1. *Based on the available literature and the findings of hypothalamic pituitary axis suppression, it appears that if patients receive only a local anesthetic agent, there are no contraindications.*
2. *If patients receive short-acting steroids, such as dexamethasone and betamethasone, a 2-week waiting period for vaccination may be appropriate.*
3. *In reference to long-acting steroids, ie, methylprednisolone or triamcinolone, 80 mg or greater, it may be appropriate to wait for at least 4 weeks prior to vaccination to avoid any interference.*

After vaccination

1. *It has been recommended to delay interventional pain procedures with steroids for 2 weeks after the second or final dose of the vaccine.*
2. *If this is not possible because several patients may be suffering from severe debilitating pain or pain that negatively affects their ability to maintain activities of daily living, we recommend to proceed with injection at the discretion of the physician and to consider using only a local anesthetic agent or the lowest possible effective dose of short-acting steroids.*
3. *Patients who are healthy, have no comorbidities, have received a single dose of vaccine, and are suffering from severe pain, which would be amenable to an interventional procedure (and this procedure cannot be delayed) may proceed with caution with a local anesthetic agent alone or with short-acting steroids.*

American Society for Interventional Pain Physicians disclaimer

These guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Because of the changing body of evidence, this document is not intended to be a "standard of care."

We assume that the physician has weighed the risks and benefits of proceeding with interventional therapy versus those of delaying the procedure and the physician has decided in conjunction with shared decision making and decided to proceed within the best interest of the patient and with their consent.

Being the largest steroid-prescribing body in the United States, the American College of Rheumatology has also published COVID guidelines as of

February 8, 2021.[25] *The guidelines acknowledge the theoretical blunting of vaccine activity as well as the risk of disease flare following vaccination, although overall, they believe that the benefits likely outweigh the risks for most patients. Based on a strong-moderate consensus, they recommended that no modification to vaccination timing schedule or steroid use be indicated for patients receiving <20 mg/day and recommended the same for those on >20 mg/day of prednisone equivalent, although only a moderate consensus was reached for this higher dosage. Recommendations regarding timing in relation with other disease-modifying agents are addressed in the guidelines but are beyond the scope of this article.*

CENTERS FOR DISEASE CONTROL AND PREVENTION RECOMMENDATIONS

The Centers for Disease Control and Prevention website, devoted to the current SARS-CoV-2 vaccine and vaccination practices, makes no specific recommendation about CSI in the perivaccination period as of this time.[26] The Centers for Disease Control and Prevention's general vaccination recommendations (not specific to COVID-19) also do not provide guidance on the use of CSI and vaccination practices.[27] However, persons receiving immunosuppression or those who are immunocompromised at or around the time of their COVID vaccination are encouraged to complete the vaccination series on schedule, and no additional doses are currently recommended at this time.

SUMMARY

Data relating CSI to the efficacy of SARS-CoV-2 vaccines do not currently exist. Although we know that CSI results in far less systemic effect than oral steroids and other immunosuppressive agents, some systemic effect does still occur. For example, physicians treating a diabetic patient with CSI typically counsel them about potential blood glucose elevation. Ultimately, there are no data showing that a CSI alone significantly impairs immune response to a SARS-CoV-2 vaccine at this time. However, guidance published by specialty societies can affect patient and physician opinions in other specialties. For example, it is now clear that patients with severe immunologic deficiency, such as that due to organ transplantation immunosuppression, hematologic malignancy, and solid tumor chemotherapy, can have an inferior response to vaccination. It is possible that specialty societies will further incorporate this newer data into their recommendations regarding CSI and vaccination, although one must be cautious in extrapolating these results because the immunologic effects of a single CSI are vastly different from the more profound immunosuppressed states described above.

Although the authors do not take a position on the specific timing of CSI relative to vaccination, perhaps the best recommendation that any society or institution can reasonably make is that patients should be counseled about evolving recommendations for CSIs and the suggested time periods espoused by various groups surrounding the period of vaccination. Practitioners should discuss the quality of evidence supporting those recommendations, given the fact that the systemic levels of steroids after CSI are relatively low at the doses used in hand surgery, but are present. The burden of the disease being treated with CSI must be weighed against its theoretical immunologic disadvantage. Corticosteroid injections, without the discussion of their theoretical impact on vaccine efficacy, may result in psychologic distress in some patients who later encounter this information on their own. We therefore recommend a case-by-case determination with informed discussion regarding the risks and benefits, recommendations such as those cited above by varying societies which may evolve over time, and allow the patient to be an informed and active decision maker regarding CSI use around the period of vaccination.

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REFERENCES

1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
3. Caillard S, Chavarot N, Bertrand D, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. *Kidney Int*. 2021;100(2):477–479.

4. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325(17):1784−1786.
5. Agha ME, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. *medRxiv*. Published online January 1, 2021. https://doi.org/10.1101/2021.04.06.21254949
6. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165−3173.
7. Shroff RT, Chalasani P, Wei R, et al. Immune responses to COVID-19 mRNA vaccines in patients with solid tumors on active, immunosuppressive cancer therapy. *medRxiv*. Published online January 1, 2021. https://doi.org/10.1101/2021.05.13.21257129
8. Wang AA, Hutchinson DT. The effect of corticosteroid injection for trigger finger on blood glucose level in diabetic patients. *J Hand Surg Am*. 2006;31(6):979−981.
9. Catalano LW III, Glickel SZ, Barron OA, Harrison R, Marshall A, Purcelli-Lafer M. Effect of local corticosteroid injection of the hand and wrist on blood glucose in patients with diabetes mellitus. *Orthopedics*. 2012;35(12):e1754−e1758.
10. Stepan JG, London DA, Boyer MI, Calfee RP. Blood glucose levels in diabetic patients following corticosteroid injections into the hand and wrist. *J Hand Surg Am*. 2014;39(4):706−712.
11. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine (Phila Pa 1976)*. 2012;37(1):E46−E50.
12. Habib GS, Miari W. The effect of intra-articular triamcinolone preparations on blood glucose levels in diabetic patients: a controlled study. *J Clin Rheumatol*. 2011;17(6):302−305.
13. Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. *Clin Rheumatol*. 2009;28(1):85−87.
14. Habib GS, Abu-Ahmad R. Lack of effect of corticosteroid injection at the shoulder joint on blood glucose levels in diabetic patients. *Clin Rheumatol*. 2007;26(4):566−568.
15. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain*. 2018;159(5):876−883.
16. Lee H, Punt JA, Miller DC, et al. FactFinders for patient safety: do corticosteroid injections for the treatment of pain influence the efficacy of mRNA COVID-19 vaccines? Accessed September 15, 2021. https://cdn.ymaws.com/www.spineintervention.org/resource/resmgr/factfinder/21/02.ff.37.covid.vax.pdf
17. Inoue S, Shibata Y, Takabatake N, Igarashi A, Abe S, Kubota I. Influence of corticosteroid therapy on the serum antibody response to influenza vaccine in elderly patients with chronic pulmonary diseases. *EXCLI J*. 2013;12:760−765.
18. Kubiet MA, Gonzalez-Rothi RJ, Cottey R, Bender BS. Serum antibody response to influenza vaccine in pulmonary patients receiving corticosteroids. *Chest*. 1996;110(2):367−370.
19. Hanania NA, Sockrider M, Castro M, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. *J Allergy Clin Immunol*. 2004;113(4):717−724.
20. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis*. 2009;9(8):493−504.
21. Kernéis S, Launay O, Ancelle T, et al. Safety and immunogenicity of yellow fever 17D vaccine in adults receiving systemic corticosteroid therapy: an observational cohort study. *Arthritis Care Res (Hoboken)*. 2013;65(9):1522−1528.
22. Russell AF, Parrino J, Fisher CL Jr, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects on chronic/maintenance corticosteroids. *Vaccine*. 2015;33(27):3129−3134.
23. Spine Intervention Society. Corticosteroid Injections and mRNA COVID-19 Vaccines. Accessed June 5, 2021. www.spineintervention.org/news/551084/Corticosteroid-Injections-and-COVID-19-Vaccines.htm.
24. American Society of Interventional Pain Physicians. COVID-19 ASIPP Updates. Accessed June 5, 2021. www.asipp.org/covid-19-asipp-updates/
25. American College of Rheumatology. COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. Accessed June 5, 2021. www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf
26. The Centers for Disease Control and Prevention (CDC). Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Accessed June 5, 2021. www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
27. The Centers for Disease Control and Prevention (CDC). General Best Practice Guidelines for Immunization. Accessed June 5, 2021. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html