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EXPERT OPINION

Recommendations and Guidance for Steroid Injection Therapy and COVID-19 Vaccine Administration from the American Society of Pain and Neuroscience (ASPN)

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Abstract: To date, COVID-19 has spread to more than 108 million people globally, with a death toll surpassing 2 1/2 million. With the United States Food and Drug Administration (FDA) approval of two highly effective COVID-19 vaccines from Pfizer-BioNtech and Moderna, we now have a novel approach to contain COVID-19 related morbidity and mortality. Chronic pain care has faced unprecedented challenges for patients and providers in this ever-changing climate. With the approval of COVID-19 vaccines, we now face questions relating to the potential effects of pain treatments utilizing steroids on vaccine efficacy. In this analysis, we address these issues and provide guidance for steroid therapies based on available data and expert recommendations.

Keywords: vaccines, chronic pain, interventional pain therapy, epidural steroid injections, COVID-19

Introduction

We continue to face one of the largest global pandemics in over a century. To date, over 28 million individuals in the United States alone have been infected with COVID-19, while over 500,000 individuals have died of the disease.[1] As we battle this global pandemic, vaccines will provide one of the most effective public health interventions that medicine and science can offer. However, critical questions are to be considered when providing interventional therapies utilizing steroids as we continue large-scale vaccine distribution. Pain medicine patients vary greatly based on the etiology of their pain—while those with pre-existing conditions such as cancer and those with rheumatoid diseases prescribed immunosuppressive agents may be severely immunosuppressed. For patients who are not immunosuppressed, there is a question regarding the clinical relevance of epidural steroids and the potential for immunosuppression. Also, there is a question of whether a steroid injection would decrease the efficacy of the COVID-19 vaccine. In order to provide guidance regarding the timing and relevance of steroid injections related to vaccination, we review the safety and efficacy of COVID-19 vaccinations in the setting of both systemic steroid and immunosuppressive agents and provide the first American Society of Pain and Neuroscience Recommendation and Guideline on this topic.

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The Impact of Epidural Steroids and Immunocompetence

Epidural steroid injections represent an integral component of modern-day pain management for many patients. The theoretical risk of immunosuppression from neuraxial steroid administration and potentially deleterious effects on vaccine efficacy is of great interest to pain providers and patients.

Glucocorticoid steroids have been considered immunosuppressive since the 1990s when it was discovered that they interfered with the signaling of inflammatory transcriptional regulators NF-kB and AP-1.[2] Acutely, glucocorticoids inhibit the vasodilatory effects from inflammation, decrease vascular permeability caused by inflammatory insults, and decrease leukocyte emigration to the site of injury.[2] Post-injury, glucocorticoid steroids affect the transcription (up- and down-regulation) of various genes in leukocytes resulting in immunosuppression and anti-inflammation.[2] Recently, studies have suggested that glucocorticoids have a pro-inflammatory effect that can restore leukocyte function in preparation for further insult.[3]

Known leukocytes affected by glucocorticoids include neutrophils, monocytes, macrophages, dendritic cells, and various T cells. These include T helper cells, which modulate antibody class switching, and natural killer cells that play a role in the defense against virally infected cells.[3] A study by Dr. Anthony Fauci demonstrated that IV hydrocortisone (400 mg) administrated to healthy adult volunteers resulted in the decreased circulation of T cells within 48 hours.[4] In a case-controlled analysis of 1947 serious infection cases in 16,207 rheumatoid arthritis patients receiving chronic oral glucocorticoids for disease management, it was found that patients taking 5 mg of prednisolone had 30%, 46%, and 100% increased risk for serious infection when using steroids continuously for 3 months, 6 months, or 3 years compared to non-users, respectively.[5]

There are significant gaps in applying data from chronic systemic exposure to epidural (neuraxial) steroid exposure. We know that steroids are systemically absorbed from the epidural space, as evidenced by post-procedure hyperglycemia and blood pressure elevation. Longer-term effects are also known, and one study determined that approximately 20% of patients experienced over 50% reduction in baseline cortisol at 3 weeks after epidural injection with methylprednisolone or triamcinolone, but not with dexamethasone or betamethasone.[6]

Specific data on the efficacy of vaccines in the setting of local steroid injection are lacking. A retrospective analysis of influenza risk among patients who received steroids in joint injections found an increased risk of viral infection, although this study was at high risk of confoundment.[7] For example, there were higher rates of autoimmune disorders, diabetes and chronic obstructive pulmonary disease among individuals undergoing joint injections. Relying on such data to guide therapeutic decision-making is scientifically questionable.[7]

While epidural steroids may be absorbed systemically, based on current dosing strategies and the pharmacodynamics of these injections, they are unlikely to demonstrate the immunosuppressive effects associated with chronic high-dose systemic steroid use.

Summary of COVID-19 Vaccine Clinical Trial Data

At the time of this writing, the US Food and Drug Administration (FDA) has authorized the emergency use of two vaccines for COVID-19, the Pfizer-BioNTech and Moderna two-dose vaccines. The Pfizer-BioNTech vaccine has an efficacy of 95%, measured from 7 days after the second dose.[8] Moderna's vaccine has demonstrated similar efficacy and is reported to be approximately 94%, measured from 14 days following the second dose.[9] While the efficacy and safety of these vaccines is well described for healthy patients, there are certain patient populations that may be hesitant to receive the vaccine based on their other medical comorbidities. One such patient population is those who are chronic pain patients routinely receiving steroid injections or prescribed immunosuppressant medications, making the timeline of when they should receive the COVID-19 vaccine unclear.

When considering the Pfizer-BioNTech clinical trial data, the manufacturer excluded patients based upon the following: anticipated needs for immunosuppressive treatment within 6 months of starting the trial, immunocompromised individuals with known or suspected immunodeficiencies, individuals with a history of autoimmune disease or active autoimmune disease, and individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (eg, for cancer or an autoimmune disease, and/or utilize inhaled/nebulized corticosteroids).[10] While these

trials excluded those utilizing systemic corticosteroids, there was no discussion of the need to exclude patients receiving more targeted steroid therapy on an elective basis. Rather, exclusion criteria emphasized the need to exclude only those who were severely immunocompromised. As for Moderna's exclusion criteria, those patients in an immunosuppressive or immunodeficient state, including HIV, asplenia and recurrent severe infections, as well as those who received systemic immunosuppressant or immune-modifying drugs for >14 days within 6 months prior to screening (for corticosteroids ≥20 milligram (mg)/day of prednisone equivalent), were all excluded from the clinical trial data.[11] These considerations are important in determining the best recommendations and practices.

Other Vaccines on the Horizon

In addition to the aforementioned approved COVID-19 vaccines, three other vaccines being considered for approval are 1) AstraZeneca (AZD1222)[12] 2) Janssen (Ad26.COV2.S)[13] and 3) Novavax (SARS-CoV-2 rS/Matrix-M1 Adjuvant).[14] All three potential vaccines are emerging with promising responses in providing immunity against COVID-19. As of December 28th, 2020, they were still in extensive Phase III clinical trials. Specific to the AstraZeneca vaccine, it is primarily designed as an adenovirus vector vaccine containing the SARS-CoV-2 spike protein's genetic material, which is a crucial element in priming the immune system and providing a robust immune response.[15] It is recommended as a two-dose regimen administered 28 days apart. In the recent interim study, results have demonstrated lower efficacy than the two currently approved vaccines in providing immunity, ie, 70.4%. As of phase III clinical trials, AstraZeneca is still actively recruiting healthy and medically stable volunteers over 18 years of age at increased risk of SARS-CoV-2 infection. Exclusion criteria include patients who are under immunosuppressed and immunodeficient states and having a significant medical disease, which was not further elaborated yet worth noting.[12]

Similar to AstraZeneca's vaccine, the Janssen vaccine in collaboration with Johnson and Johnson also developed a non-replicating adenoviral vector vaccine for adults age>18 years. The phase III clinical trial (ENSEMBLE) used a single-dose regimen. Ninety-seven percent of participants were determined to be positive for neutralizing antibodies against SARS-CoV-2 on the 29th day following the vaccination. The majority of adverse events reported were mild to moderate, classified as grade 1 and grade 2 in severity. There are no exclusion criteria specific to immunosuppression worthy of noting.

Novavax is a current emerging vaccine similar to spike protein vaccines with saponin-based matrix-M adjuvant and without M adjuvant. It is known as NVX-CoV2373 and requires a two-dose regimen given 21 days apart, which is currently in phase III clinical trials (PREVENT-19).[16] Examining the exclusion criteria, it is worth noting that chronic administration of steroids (defined as >14 days, systemic glucocorticoids, other immune modifying drugs within 90 days prior to the initial study vaccination, receiving any immunoglobulins, or blood-derived products prior to first study vaccination), autoimmune diseases, and participation in research involving drug/biologic/devices within 45 days prior to the initial study vaccination excluded patients from participation in the PREVENT-19 trial.[14]

Key Conclusion from Vaccine Trial Data Exclusion Criteria

Across the board outside of the Johnson and Johnson vaccine, it is clear that systemic immunosuppression patients were excluded. Specifically, in the Moderna trial, it is to be noted that systemic treatment constituted taking corticosteroids ≥20 milligram (mg)/day. However, specific considerations to the mode of steroid administration were not specified in any of the current vaccine trials as well as the more specific definition of the level of immunosuppression outside of the Moderna trial.

Safety of Vaccination in the Setting of Systemic Steroid Use

With respect to safety, corticosteroid use is a concern in the setting of live vaccination and at systemic doses equivalent to 2 mg/kg or a dose of 20 mg per day of prednisone equivalents for 2 or more weeks.[17–19] While there are some live attenuated COVID-19 vaccines under development internationally, these are not among the leading vaccines for distribution in the USA and will not be discussed further for the purposes of this review. At present, the two SARS-CoV-2 vaccines that have been granted FDA Emergency Use Authorization do not employ live viruses and therefore are not anticipated to pose special safety concerns with respect to immunocompromised hosts. As discussed above, several vaccines in development deliver recombinant protein through an

adenovirus vector, the most advanced of which is the Oxford/AstraZeneca ChAdOx1 nCOVID-19, which may gain approval within the United States as early as March or April of 2021. Adenovirus vector vaccines are considered appropriate for use in immunocompromised hosts because there is no risk for reversion to a virulent SARS-CoV-2 strain as may be the case with traditional live vaccines. Overall, there is no evidence that patients receiving spinal steroid therapy for the management of pain are at increased risk of adverse outcomes from COVID-19 vaccination.

Efficacy of Vaccination in the Setting of Systemic Steroid Use

The primary concern regarding COVID-19 vaccines in the setting of steroid use is efficacy given the immunosuppressive hallmarks of corticosteroids. These include direct effects on critical components of vaccine-based immunity, such as antigen presentation, T/B cell function and antibody generation. Almost 50 years ago, some of the first observations of steroids on the adaptive B cell responses, the primary mechanism of vaccine protection, were described by Dr. Anthony Fauci and colleagues. These included transient declines in lymphocyte populations with supraphysiologic dosing,[20,21] lymphocytic apoptosis, predominantly T cell, and altered immunoglobulin secretion,[22,23] and either suppression or stimulation. There exists considerable evidence in animal models that corticosteroids can influence both B cell development and function once in the periphery,[24] although the implications of such on vaccine responses are not clear.

While our understanding of how steroids affect T and B cells continues to evolve, there are currently more data on functional vaccine outcomes in the setting of chronic steroid use. Decreased serologic responsiveness and disease protection have been demonstrated in pneumococcal vaccines at doses of 20 mg of prednisone or greater per day.[25] There has also been evidence of delayed responsiveness to Hepatitis B vaccination[26] in children on high dose steroid therapy for nephrotic syndrome and in influenza vaccination among cancer patients on systemic steroids.[27] While these findings suggest that chronic high dose steroids may impair vaccine-based immunity, the effect on efficacy in these studies was small. Further, short-term systemic bolus steroids have not been demonstrated to impact vaccine responsiveness. This has been the case for tetanus[28] and influenza.[29,30] Further, inhaled steroids do not appear to affect serologic responsiveness to Hepatitis B vaccination.[31]

Broader Considerations on the Impact of NSAIDs and COX-Inhibitors on Immunity and Vaccine Efficacy

Non-steroidal anti-inflammatory drugs are a common alternative to opioids in pain medicine. NSAIDs demonstrate their anti-inflammatory effect by modulating cyclooxygenase enzymes COX-1 and COX-2. Despite COX-2 being an inflammatory mediator, studies have demonstrated its role in producing antibodies in activated B lymphocytes. Of the commonly used NSAIDs such as ibuprofen, indomethacin, and aspirin, indomethacin exerts some significant effects in inhibiting human B-lymphocytes and B-lymphocyte IgM, IgG synthesis. Acetaminophen, aspirin, and naproxen have demonstrated similar results in knocking out antibody production when used at pharmacologic doses. Studies have demonstrated a directly proportional relationship between increased dosages of NSAIDs and reduced production of immunoglobulins. In addition to their anti-inflammatory effect, NSAIDs exert immunomodulatory effects by interfering with human monocyte and T-lymphocyte activation, proliferation, and cytokine synthesis. Specific to the impact of NSAIDS on vaccine efficacy, Jackson and colleagues determined that low dose aspirin did not affect the efficacy of H1N1 influenza vaccine in elder adults.[32] An analysis by Saleh et al mentioned that studies have shown that acetaminophen-associated antibody blunting has still resulted in protective antibody levels.[33] Further research is needed to specify the effects of NSAIDs' dosages and frequency of use on the immune response in the context of vaccine administration. Overall, the data are inconclusive and insufficiently robust to draw meaningful conclusions and change potential practice algorithms.

Ethical Considerations and Timing of Therapeutic Pain Interventions

In patients with severe immunodeficiency risks including chemotherapy, transplant and autoimmune disorders, decisions regarding vaccine administration versus treatment delay can be clarified by the perceived severity of the underlying condition for which the patient is receiving steroids. Some may argue that interventional treatment

for pain can be delayed or is elective, particularly during a severe pandemic.[34] However, such an approach fails to account for individual patients' unique experiences of their pain and their perceived urgency for achieving at least a modicum of relief. The individual and societal tradeoffs associated with delays in standard medical care have been made starker during the past year due to the coronavirus pandemic. The opioid epidemic, in particular, has grown in magnitude in part due to restricting access to critical pain management care[35] as well as barriers to access to substance use disorder treatment.[36] As discussed above, the literature on the impact of spinal procedures on COVID-19 vaccination is supportive of concomitant virus prophylaxis and interventional pain management, although as is often the case in medicine, 100% safety has not as yet been empirically established. Undoubtedly, patients requiring spinal procedures for pain control should be provided with sufficient education that allows them to provide informed consent should they choose to pursue concomitant COVID-19 vaccination and interventional spine procedures. Further, we cannot ignore that much of the patient population who require spinal procedures for pain control are at high risk for COVID-19 infection based on age and medical comorbidities. As it is likely that pursuing both COVID-19 vaccination and interventional pain procedures will not endanger these vulnerable patients, we recommend that vaccines not be deferred in this population based on any ethical grounds.

Summary Recommendations

The following are the summary recommendations and guidelines based on the aforementioned data and evidence. We want to acknowledge that the following recommendations are fluid and will be updated based on ongoing data. We would also recommend that physicians determine each individual patient's level of acuity and weigh out specific risks/benefits while applying these broad recommendations set forth.

1) 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.

2) There is no evidence that bolus steroids in the epidural space will impact vaccine responsiveness.

3) Neuraxial steroid injections do not need to be deferred when indicated in the context of COVID-19 vaccination.

4) No specific guidance suggests withholding NSAIDs or other anti-inflammatories prior to receiving vaccination.

Conclusion

There is no current evidence that epidural steroid therapy will impact the efficacy of the COVID-19 vaccine or place the patient at increased risk of adverse effects from the vaccine. Previous data demonstrate that chronic high-dose steroids may impair vaccine-based immunity, although the decrease of vaccine efficacy in these settings was small. Steroids given systemically in bolus format have not been demonstrated to impact vaccine efficacy. Thus, while many pain providers may be concerned with the effects of epidural steroid injections on vaccine safety and efficacy, there are no data that suggest epidural steroid injections should be postponed or avoided due to COVID-19 vaccination. However, given the lack of direct evidence of COVID-19 vaccine efficacy in combination with these therapies, it is reasonable for clinicians to consider individual patients' risks in modifying pain treatment plans including dosing strategies, steroid selection and treatment timing. These considerations should include factors such as the urgency of the procedure, coexisting medical conditions such as concomitant immunosuppression as well as the risks of alternative pain management strategies or suboptimal pain control. We believe that providing interventional pain treatment concomitantly with vaccination against the coronavirus represents sound medical practice, provided that patients choosing to pursue both treatments understand that the safety and risk data, at this point, are not yet sufficient to completely rule out interactions in some patients. However, depriving suffering patients of either treatment is associated with its own ethical pitfalls.

Disclosure

Dr Krishnan Chakravarthy is a consultant for Medtronic, Vivex Biologics, and PainTeq, outside the submitted work. Dr Michael E Schatman is a research consultant for Firstox and Modoscript, outside the submitted work. Dr Timothy Deer reports personal fees from Abbott, Flowonix, Mainstay, Ethos, Stimgenics, SI Bone, Nevro, Medtronic, and PainTeq; owns stock options from Vertos Medical, Axonics, SpineThera, Saluda Medical, Nalu, Vertiflex, Cornerloc, SPR Therapeutics, and Boston Scientific, outside the submitted work. In addition, Dr Timothy Deer has a patent Abbott – DRG Surgical Leads pending. The authors report no other conflicts of interest in this work.

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