OHSIPP GUIDANCE DOCUMENT ON COVID-19 VACCINE AND STEROIDS
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The Ohio Society of Interventional Pain Physicians (OHSIPP) has received numerous requests for guidance regarding the use of steroid injections during COVID-19 and specifically guidance on the use of steroids in injections, before and after being vaccinated against the coronavirus that causes COVID-19.

When considering any possible concerns for using steroids around the time of any vaccine administration, it is important to understand how vaccines work and that there are different types of vaccines. This will lead to different types of interactions and concerns.

We will briefly review vaccines and discuss the types of vaccines currently used. Vaccines are used to help the body fight off diseases caused by infections from viruses and bacteria. Recall that when a germ, either a virus or bacteria, invades the body, they multiply to create illnesses and infections. The body's immune system will then try to mount a response using the white blood cells present in the bloodstream and tissues. The white blood cells consist of macrophages, B-lymphocytes and T-lymphocytes. The macrophages are the first line of defense and will absorb and digest the germ and damaged cells. These are then digested and the remaining debris will include parts of the germ that are recognized as foreign: the antigens. B-cells will investigate the antigens and produce antibodies to recognize and attack the germ. T-cells are "attack" cells that will recognize and remove the germ and infected and damaged cells in the body. After the initial infection and if the body survives it, the immune system now has the antigen

in its memory and will recognize future invasions by that specific germ in order to attack and neutralize it before a dangerous infection can develop.

When a vaccine is administered to a patient, the vaccine mimics an infection. Foreign antigens specific to a disease-causing germ are presented to the body, which then mounts an immune response. This immune response should be sufficient enough to activate B-cells to produce antibodies and create T-cells with memory to recognize and attack the foreign invader and damaged cells. Ideally, the vaccine is not able to create a "true" infection in the patient, and in a few weeks, the body will develop adequate immunity to the germ. It is, thus, possible that a person may become infected with the same illness for which he was vaccinated, in the days before or after the vaccination (1).

There are three classic categories of vaccines and a newer fourth category, known as mRNA and DNA vaccines (2). The four types of vaccines are detailed below:

1. Vaccines with the virus present in an attenuated-live, or inactivated-dead, form.
2. Vaccines with parts, or subunits, of the germ in the injectate.
3. Toxoid vaccines contain the toxin produced by bacterial infections (diphtheria and tetanus). These are not applicable to viral infections and will not be discussed further.
4. mRNA and DNA vaccines, the "newest" category of vaccines, carry harmless genetic material, such as messenger RNA or DNA which carries the genetic code to make a subunit of the virus (3).

Vaccines with the pathogen virus present, may have (weakened) live or dead viruses. The live virus will produce a better immune response than the dead virus (2). The concern with these vaccines is whether a live virus can produce a true infection in some people, particularly immune-supressed patients. Examples of live virus vaccines include measles, mumps and rubella (MMR) and chickenpox. Dead virus vaccines include hepatitis A and flu.

Subunit vaccines include parts of the virus that are easily recognizable, such as proteins and polysaccharides present on the germ's surface (2). The advantage of these vaccines is that there is no complete germ present that can produce an infection or disease. This is important as they can be given to people who are immune-suppressed. Subunit vaccines include hepatitis B, human papillomavirus and shingles.

mRNA and DNA vaccines introduce genetic material into the body to then make the host produce subunits of the virus. In the case of the COVID-19 virus, a prominent protein spike protrudes from the virus coat. The mRNA vaccines carry messenger RNA specific to the production of this protein spike. When the vaccine is administered, the host cells then begin to read the code and produce the protein spike. The mRNA is short-lived and breaks down in the body on its own (3). The foreign protein spike appears on host cells and is attacked by the body. This starts the immune response cascade. The concept and technology of mRNA vaccines has existed since the 1980s (5). The genetic sequence of the COVID-19 virus was discovered and released in January 2020 (6). This then enabled vaccine scientists to understand the genetic sequence for the protein spike and apply knowledge and technology of mRNA vaccines to the COVID-19 pandemic. Because of the urgency of the COVID-19 pandemic, these vaccines were expedited through development and investigation. On December 11, 2020, the U.S. Food & Drug Administration granted emergency use authorization (EUA) to the first mRNA COVID-19 vaccine, developed by Pfizer and BioNTech (7). In the United States, the first two COVID-19 vaccines available

were produced by Pfizer/BioNTech, Moderna(8). Johnson & Johnson has a DNA vaccine which became the third COVID-19 vaccine available in the US. In the case of the Johnson & Johnson vaccine, an adenovirus vector introduces the DNA sequence into the patient's cells, which then produce the protein spike (9). The adenovirus used in the Johnson & Johnson vaccine is not pathogenic and is unable to replicate.

The urgency of the COVID-19 pandemic has resulted in many nations and companies offering potential vaccines against the disease. There are now potential vaccines from all the major vaccine categories. This list is not meant to be complete but to give some idea of the variety of COVID-19 vaccines available across the globe. The provider should take into consideration the vaccines currently available in their region, when trying to ascertain any possible interactions between injected steroids and COVID-19 vaccines. Some examples of COVID-19 available, and in development, across the globe include (4):

1. Attenuated and inactive virus vaccines: China has investigated several vaccines containing inactivated (dead) COVID-19 virus. They include the Coronavac (also known as Sinovac) and New Crown vaccines (10, 11).
2. Subunit vaccine: The Novavax is a vaccine made using recombinant technology to create virus subunits (12).
3. mRNA and DNA vaccines: These vaccines include the versions by Pfizer, Moderna and Johnson & Johnson (7, 8, 9).

Currently, three vaccines are approved in the United States; Pfizer and Moderna which are both mRNA vaccines and Johnson & Johnson which uses DNA transmitted by an adenovirus. These vaccines do not contain live coronavirus capable of causing a COVID-19 infection. Additionally, patients who are immuno-compromised and even patients who have stable HIV, were enrolled in the clinical trials needed for approval.

Corticosteroid-related immunosuppression has been discussed since the 1950s (13). However, corticosteroid-related immunosuppression has not been a significant consideration in interventional pain management prior to the COVID-19 era, with substantial discussions and concerns about the effects of injectable steroids on the immune system (14-17). Interventional pain physicians administer steroids for various procedures, including epidurals and intraarticular injections. The steroid use has been shown to increase the risk of influenza (18); however, there are no studies regarding COVID-19, and it has been speculated that steroids might have a beneficial effect on the course of COVID-19, even though steroids can be immunosuppressive (19). Initial reports showed the beneficial effect of steroids. In fact, a systematic review and meta-analysis of 7 clinical trials across 12 countries have concluded that corticosteroids are associated with lower mortality among critically ill patients with COVID-19 when compared to the usual care or placebo (20). Despite this comforting news, OHSIPP guidelines and multiple other guidelines caution against using steroids during the COVID-19 season, and many of the practices have curtailed using the steroids, or are using in low doses (15-17,21).

One of the main side effects of steroids is hypothalamic-pituitary-adrenal (HPA) suppression (17). Friedly et al (22) showed that patients treated with methylprednisolone or triamcinolone had an average 3-week cortisol reduction of 41% and 41.6% from baseline, respectively. Further comparison with patients treated with betamethasone or dexamethasone, found no significant changes with cortisol and they were similar lidocaine alone. Hooten et al (23) showed that terminal elimination half-life of lumbar epidurally administered triamcinolone in a noncompartmental analysis was 22 days and the peak times in concentration was detected within 24 hours after administration. Abdul et al (24) in 2017, reported that after one epidural injection of 80 mg of methylprednisolone, 87% of patients exhibited HPA axis suppression at day 7 post injection, 43% at day 14, and 7% at day 28. Habib et al (25) in 2013, found a dose-dependent effect in a study examining the magnitude and duration of this suppression of the single epidural injection

of methylprednisolone, with 86% of patients exhibiting HPA suppression with 80 mg dosage and 53% with 40 mg of dosage, with 20% of all participants continue to have suppression at 4 weeks post injection. Consequently, it is presumed that endocrine disruption from a single epidural steroid injection suggests similar systemic effects on immune response.

Adverse immune influences of corticosteroids during influenza infection is of increased concern for those prescribed or injected with corticosteroids, with specific concerns during the current COVID-19 epidemic. Meta-analysis of early-administered corticosteroids versus placebo demonstrates an increased risk of influenza infection within the steroid group. A dose-dependent relationship for infection risk has been demonstrated showing a relative risk of 1.5 with low-dose steroids and a relative risk of greater than 8, with doses above 40 mg per day (26). In fact, a single dose of corticosteroids have shown an increased incidence of influenza infection associated with steroid injection compared to no injection (15). The Advisory Committee on Immunization Practices (ACIP) (27) and the Centers for Disease Control and Prevention (CDC) (28) advised to defer live vaccination at least one month after discontinuation of high-dose systematically absorbed with glucocorticoid therapy administered for 14 days.

There has long been controversy about the potential effects of steroid use around the time of any vaccination. In the case of interventional pain management, steroids are used to reduce inflammation and stabilize nerve membranes that may play a role in pain. With the imminent vaccination of large populations across the globe against COVID-19, interventional pain management specialists should be aware of the concerns related to possible interactions between COVID-19 vaccines and steroid use.

First, there are different types of vaccines and the concerns related to steroid use differ based on vaccine type. The common concern is that steroids can suppress the immune system in patients and this will affect the response to the vaccine. There are essentially two areas of concern when discussing steroid-induced immunosuppression and vaccines. First, and most concerning is that, in live vaccines, a suppressed immune system may allow the live vaccine to take hold and cause an infection and disease in the vaccinated patient. This is only a concern if live-attenuated virus is used in the vaccine. The current COVID-19 vaccine trials, of vaccines with virus in the injectate, are using the inactive or dead form of the virus, so this should not be an issue or real concern.

The second common concern is that the steroid will suppress the inflammatory immune response and impair the movement of glucophages into the vaccinated tissue and the activation of B-lymphocytes and T-lymphocytes, resulting in the production of fewer antibodies. Studies show that glucocorticoids can have an enhancing and suppressing effect on macrophages, B-lymphocytes and T-lymphocytes. Steroids have been shown to slow the movement of macrophages toward damaged or infected tissue, but can also increase the number of circulating neutrophils in the bloodstream (29,30). Since the COVID-19 vaccines are so new, there is no scientific evidence to show that steroids have any impact on the production of antibodies after vaccine administration.

We cannot say that steroids administered to a patient 2-4 weeks before or after a vaccination with any of the potential COVID-19 vaccines will interfere with the development of adequate antibodies against this disease. Given the danger of the disease and the cost of the worldwide vaccine effort, it is wise to give priority to the effort to vaccinate the population and encourage patients to proceed with and complete their vaccination against COVID-19 as soon as it is offered to them. If a pain management steroid injection is being considered in an elective scenario, it can be delayed until after the patient has finished their COVID-19 vaccination sequence, which will depend on whether the particular vaccine entails one or two shots. If the patient has significant pain and cannot wait, then an effort should be made to schedule

steroid injections approximately 2 weeks before the first dose and approximately 2 weeks after the last dose. The exact time frame would depend on the dose, potency and duration of action of the steroid to be injected.

With lack of appropriate guidance from authorities, with multiple questions, we have developed this guidance document.

However, what remains to be uncertain is whether or not steroid use around the time of actual vaccine administration would somehow hinder or negatively impact the efficacy of a vaccine.

BEFORE VACCINATION:

It is recommended by OHSIPP that physicians follow the risk mitigation guidance statement put out by OHSIPP regarding the use of corticosteroids and completing procedures in the COVID-19 era (3,4,9). This guidance statement stratifies the risk based on comorbidity and potential morbidity mortality related to the virus itself.

1. If patients are to receive any steroids, a 2-week waiting period for any COVID-19 vaccination may be appropriate.

2. No wait is needed for injections or interventions not requiring steroids, such as local anesthetic-only injections, viscosupplement injections, botulinum toxin injections or regenerative medicine interventions.

AFTER VACCINATION:

1. It may be appropriate to ***delay interventional pain procedures with steroids*** for two weeks after any COVID-19 vaccine.
2. A steroid injection could thus be offered approximately two weeks after the first vaccination, and approximately two weeks before the second and final vaccination, when two vaccines are required to complete the sequence.

In patients suffering from severe debilitating pain or pain that negatively impacts their ability to maintain activities of daily living, ***we recommend to proceed with the injection, at the discretion of the physician and to consider using the local anesthetic only or lowest possible effective dose of short-acting steroids***.

DISCLAIMER:
These guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Due to 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 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 consent.

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