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## Should I use steroid injections to treat shoulder pain during the COVID-19 pandemic?



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Corticosteroid (CS) injections are commonly used both in primary and secondary care in the management of chronic shoulder pain. On March 11, 2020, the World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative virus for COVID-19) outbreak a pandemic and global health emergency. There was initial concern with the use of CS injections during the COVID-19 pandemic because of the increased potential for adrenal insufficiency and altered immune response. This led to the publication of guidelines from societies around the world. The aim of this article is to critically appraise the evidence that form the rationale behind these guidelines and to review the alternative treatment options for the management of shoulder pain during the COVID-19 pandemic.

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Corticosteroid (CS) injections are commonly used both in primary and secondary care in the management of chronic shoulder pain. On March 11, 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative virus for COVID-19) outbreak a pandemic and global health emergency.<sup>29</sup> There was initial concern with the use of CS injections during the COVID-19 pandemic because of the increased potential for adrenal insufficiency and altered immune response. This led to the publication of guidelines from societies around the world.

The only national guidelines issued in the United States was a joint statement on March 27, 2020, by the American Society of Regional Anesthesia and Pain Medicine and European Society of Regional Anesthesia and Pain Therapy that advised against elective pain procedures and recommended that clinicians “consider evaluating risks/benefits of steroid injections and use a decreased dose, especially in high-risk patient populations.”<sup>1</sup> In the United Kingdom, the National Health Service in collaboration with the British Association of Orthopaedics and other societies published guidelines on March 23 that were further updated on June 16, 2020, advising to avoid the use of CS injections in the management of

musculoskeletal and rheumatic conditions during the COVID-19 pandemic.<sup>3</sup> The Australasian Musculoskeletal Imaging Group issued a response on March 25, 2020, “recommending that members continue to perform image-guided corticosteroid injections during the COVID-19 pandemic where they are clinically indicated following informed consent.”<sup>23</sup>

The conflicting nature of these guidelines can pose difficulties for the clinician in determining best practice for treatment of shoulder pain during the COVID-19 pandemic. The aim of this article is to critically appraise the evidence that form the rationale behind these guidelines and to review the alternative treatment options for the management of shoulder pain during the COVID-19 pandemic.

### COVID-19: physical therapy and nonsteroidal anti-inflammatory drugs

The first line of treatment for shoulder pain is usually nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy. It is, however, important to consider the implications of the COVID-19 pandemic on these treatment options. There were initial reports on the possible adverse effects of the use of NSAIDs in acute respiratory tract infections and subsequent concern in relation to COVID-19. Nevertheless, there is currently no evidence that the acute use of NSAIDs causes an increased risk of developing COVID-19 or developing a more severe COVID-19 disease.<sup>28</sup> Current guidance advises patients to continue using NSAIDs for chronic conditions.<sup>15</sup> It is important that patients with musculoskeletal disorders are aware of

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this information as there is conflicting information in the media that may influence patients' medication adherence.

In the light of the COVID-19 pandemic, significant changes have been made to physical therapy services, with a greater emphasis on telemedicine and reduction in face-to-face consultations. Patients are often directed to online resources, to help them manage their symptoms, including home exercises.

### CS injections and shoulder pain

Although there is no clear evidence for the long-term effectiveness of CS injections in the management of chronic shoulder pain,<sup>12,14,24</sup> the rationale for their use is to provide transient pain relief that will facilitate rehabilitative and strengthening exercises.<sup>4</sup> The mechanism of action of CS in reducing pain is not fully understood; however, it is thought to be secondary to both an immunosuppressive and anti-inflammatory effect. CSs act directly on nuclear steroid receptors and disrupt the inflammatory and immune cascade at different levels. This results in reduced vascular permeability, the inhibition of accumulation of inflammatory cells, and the prevention of synthesis and secretion of multiple inflammatory mediators such as leukotrienes and prostaglandins. This anti-inflammatory effect results in a reduction in swelling and an increase in the concentration of hyaluronic acid (HA).<sup>10,17</sup>

### CS injections and COVID-19

The current guidance in the United Kingdom recommends that CS injections should be avoided during the COVID-19 pandemic. The guideline states that the potential arises to do harm in injecting CSs in individuals who may be incubating or later develop COVID-19, as these patients may remain asymptomatic for up to 10 days. The guidelines recommend simple analgesia, activity modification, and exercise as first-line management in most patients with noninflammatory musculoskeletal pain.<sup>3</sup> Intra-articular CS injections, however, can be considered if patients have high levels of pain and disability, have failed first-line measures and if continuation of these symptoms will have a significant negative effect on their health and well-being.<sup>3</sup> It is noteworthy that the WHO has not issued specific guidelines on the use of CS injections during the pandemic. The only guidance from WHO with regard to CSs is to avoid using them in the clinical management of severe acute respiratory syndrome infection when COVID-19 infection is suspected.<sup>27</sup> However, this guidance is likely to be updated to reflect the results of the Randomised Evaluation of COVID-19 therapy (RECOVERY) Trial.<sup>9</sup>

So why have guidelines in the United States and United Kingdom advised caution to the use of CS injections? We have tried to analyze the evidence that form the basis of these guidelines and highlighted the potential alternative options in managing chronic shoulder pain. The evidence for avoiding the use of CS injections can broadly be subdivided into 3 categories: (1) evidence from previous pandemics, (2) evidence from studies on influenza virus, and (3) CS-induced secondary adrenal insufficiency.

### Evidence from previous and current pandemic

Systemic CSs were widely used to treat acute lung injury and acute respiratory distress syndrome during the outbreaks of severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV).<sup>18</sup> The administration of systemic CS was shown to delay viral shedding in some cases and was more likely to cause harm than be of any benefit.<sup>18,20</sup> It has to be noted that the CS dose used in these studies was significantly higher than that used in intra-articular or soft tissue injections.

When the initial guidelines from the National Health Service England and the American Society of Regional Anesthesia and Pain Medicine were released advising caution with the use of intra-articular steroid injections, there was only 1 published study that had evaluated CS treatment in patients with COVID-19 infection.<sup>31</sup> In this observational study, 11 of the 31 patients (median age 39) infected with COVID-19 were administered CS (40 mg prednisolone twice a day for 5 days). Patients receiving CS were clinically more symptomatic on presentation, had higher inflammatory markers, and had more significant abnormalities on chest computed tomography compared with patients who did not receive CS. The authors concluded that the administration of CS did not influence virus clearance time or duration of symptoms in their cohort of patients with mild COVID-19.<sup>31</sup> The findings of this study should be interpreted with caution when extrapolating the results to the field of musculoskeletal medicine. For example, the median age of patients in this study was considerably lower than that of the typical musculoskeletal patient population, and the CS dose was significantly higher than that used for musculoskeletal injections.

Although intra-articular CS injections are administered locally at 1 or more joints, a significant amount of the injected compound can be absorbed, resulting in significant detectable serum levels over days to weeks following the injection.<sup>7</sup> Furthermore, the possible systemic effects of intra-articular CS injections may be similar to that following oral or intravenous administration.<sup>7</sup> It is therefore plausible that the administration of CS injections could result in a delay in viral shedding in asymptomatic patients infected with COVID-19. Nevertheless, early results from the RECOVERY trial demonstrate dexamethasone to reduce 28-day mortality in hospital patients receiving invasive mechanical ventilation or oxygen with COVID-19.<sup>9</sup>

### Evidence from studies on influenza virus

A recent meta-analysis demonstrated that the use of systemic CS increased mortality, length of stay in intensive care unit, and rate of secondary bacterial infection in patients with influenza virus-induced pneumonia.<sup>16</sup> The authors concluded that one possible reason for these findings could be the deleterious effect of CS on inhibiting the immune responses mediated by B and T cells. The alterations in immune reactions caused by CS may have prolonged viremia and delayed viral clearance, thus increasing the risk of mortality.

Another study evaluated the effects of CS injections on the effectiveness of the influenza vaccine.<sup>21</sup> The aim of the retrospective study was to determine the rate of influenza in patients receiving a hip, knee, or shoulder CS injection just before or during the 5 influenza seasons between August 2012 and March 2017.<sup>21</sup> A total of 15,068 CS injections were performed. Vaccinated patients who had received a major-joint CS injection were found to be at increased risk for developing influenza compared with vaccinated control patients. The risk was particularly high in women younger than 65 years. Based on this study, CS joint injections performed just before or during the influenza season appeared to confer an independent risk with a relative risk of 1.52.<sup>21</sup>

### CS-induced secondary adrenal insufficiency

A bidirectional communication exists between the brain and immune system, in which the immune system signals the brain via cytokines and the brain, in turn, regulates the immune system, in part through the action of the hypothalamic-pituitary-adrenal (HPA) axis with resultant release of cortisol.<sup>13,26</sup> This axis is self-regulated, with cortisol feeding back to the hypothalamus and pituitary to downregulate the HPA axis. Cortisol not only regulates

the immune system but it is also essential for the regulation of several homeostatic mechanisms in the body, including the central nervous system, cardiovascular system, and metabolic homeostasis.

During many bacterial and viral infections, the HPA axis is activated, resulting in an increase in the circulating cortisol levels.<sup>25</sup> This HPA axis activation and resultant cortisol response are critical for the survival of the host, and interruption of the axis can potentially exacerbate the severity of the infection and in some cases increase the mortality rate.<sup>25</sup>

There are numerous reports that show the administration of intra-articular CS injections can lead to suppression of the HPA axis and secondary adrenal insufficiency.<sup>7,11</sup> Following an intra-articular CS injection, there is a rapid reduction in serum cortisol levels, within hours, to very low or unmeasurable levels. Serum cortisol levels usually stay low for 2 days but may continue to be at reduced levels for up to 4 days.<sup>7</sup> The level and duration of suppression are dependent on many factors, including the type of CS injected, depot preparation, dose, type of joint, and number of joints injected.<sup>7</sup> During the time of recovery of the normal HPA axis function, the patient is potentially vulnerable to life-threatening adrenal insufficiency during times of stress such as illness.<sup>7,11</sup>

All CSs injected into a joint show passage into the systemic circulation, resulting in adrenal suppression, but the duration of suppression is longer with methylprednisolone and triamcinolone compared with betamethasone or dexamethasone.<sup>5–7</sup> If there was an absolute need for a CS injection during the pandemic, it would therefore be sensible to consider the use of betamethasone or dexamethasone rather than methylprednisolone or triamcinolone.

#### Alternatives to CS injections

There are a number of alternatives to CS injections for shoulder pain which include HA, platelet-rich plasma, and prolotherapy.

HA is physiologically present in synovial fluid; its main functions are to lubricate the joint as well as mechanically protect the joint by acting as a shock absorber and by stabilizing the articular cartilage against shear forces.<sup>22</sup> Some patients with severe COVID-19 pneumonitis may develop acute respiratory distress syndrome, and previous studies have shown that HA is associated with acute respiratory distress syndrome, and during SARS infection the production and regulation of HA is defective.<sup>8,30</sup> The inflammatory cascade has been shown to increase the production of HA, with HA having the ability to absorb water up to 1000 times its molecular weight.<sup>2</sup> This can contribute to the appearance of “lungs of wet drowning” that have been demonstrated in autopsy reports on COVID-19 patients.<sup>30</sup> Hence, it has been suggested that reducing the presence or inhibiting the production of HA may improve the breathing in COVID-19 patients.<sup>19</sup> We have found no studies that have assessed the relationship between HA injections and increased risk of contracting COVID-19. The relevance of the above studies in the context of HA injections for musculoskeletal conditions remains unknown. To our knowledge, there are no published guidelines on the use of platelet-rich plasma therapy or prolotherapy during the COVID-19 pandemic.

#### Conclusion

This review has shown that the true impact of CS injections on a patient's immunity during the COVID-19 pandemic remains unclear. Although administration of intra-articular CS injections may have systemic effects, we found no strong evidence to suggest that this increases the risk of contracting COVID-19 or alters the clinical course of an infection in asymptomatic carriers of the virus.

Although caution is recommended based on the indirect evidence, further studies are required to determine the correlation between administration of CS injections and risks of contracting COVID-19. Patients with unremitting pain who have exhausted all other treatment options can be offered CS injections after shared decision making. Patients should be counseled about the theoretical risk of CS-induced immunosuppression and subsequently contracting COVID-19. If the patient decides to proceed with the CS injection, it would be advisable to use betamethasone or dexamethasone because of the shorter period of adrenal suppression. Nevertheless, the results of the RECOVERY trial are encouraging for the use of CSs in those critically unwell COVID-19 patients.<sup>9</sup>

Patients who elect not to have the CS injection or patients deemed to be at higher risk from the coronavirus can be offered alternative injection therapies. Some studies have shown that increased HA production may be associated with breathing difficulties in patients with COVID-19 infections. The relevance of these studies in the context of HA injections for musculoskeletal conditions remains unknown, and further clarification is needed to assess if HA injections can be safely administered during the current pandemic. Platelet-rich plasma and prolotherapy appear to be suitable effective options in the management of some causes of shoulder pain, and we found no contraindications to their use during the current pandemic.

#### Disclaimer

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