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EDITORIAL

COVID-19: A rethink of corticosteroid injection?

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Corticosteroid injection (CSI) is a mainstay of treatment for many musculoskeletal conditions. We are concerned with the apparent wholesale withdrawal of CSI as a legitimate treatment option for patients who are suffering from hand, wrist and other musculoskeletal conditions during the COVID-19 pandemic. As patients suffer and routine operating (based on the COVID-19 triage system) seems months away, surgical alternatives are unlikely to be available, and indeed it is good practice to consider an injection before committing to surgery (which is often a requirement prior to funding in the NHS). For hand-related conditions such as nerve compression, base of thumb arthritis and several tendon-related pathologies (trigger digit and de Quervain's), there are few reliable alternatives.

The onset of the current COVID-19 viral outbreak prompted appropriate reviews of clinical services and practice to prevent patients from attending healthcare institutions, in particular those with underlying conditions that would render them vulnerable to severe viral infection, in order to minimize the spread of the COVID-19 virus and to allow hospitals and healthcare services to realign their focus in order to prevent the available resources from being overwhelmed. Given the potential immunosuppressive effects of CSI, various national professional bodies issued guidance surrounding the safety and appropriateness of its use as a part of this national effort, discouraging clinicians from offering CSI as a treatment modality.[1-4] The rationale underpinning the published guidance appears to have been influenced by observations which were attributable to the administration of systemic corticosteroids during previous Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome and influenza epidemics.[1-4] While close reading of the published guidelines shows they have recommended a cautious risk-benefit analysis on a case-by-case basis, in practice the guidance has been widely interpreted as representing an instruction to cease CSI to treat most musculoskeletal conditions.

Given the true impact of CSI on a patient's immunity during the outbreak remains poorly understood, as patients return to seeking treatments for their painful and debilitating musculoskeletal conditions, it is increasingly important to determine which treatments can and should be offered to them, balancing the risks of CSI against the established efficacy of the injections, and the relatively unavailable surgical alternatives. We have therefore critically appraised the literature and evidence that the British Pain Society, British Society of Skeletal Radiology (BSSR), and other societies have used when generating their respective guidance in order to inform clinicians when counselling patients who present to them for treatments now that the initial peak of COVID-19 epidemic appears to be passing.

The cited papers describe safety concerns related to injections and changes to recipients' systemic physiology resulting from the exogenous steroid. In a paper looking at the effects of epidural CSI, Friedly et al[5] observed that adrenal suppression occurred following injection with no relationship to other patient characteristics, although reported that only 1/149 suffered an adverse event that could have potentially related to immunosuppression (pneumonia) despite the relatively high steroid doses being used (up to 120 mg methylprednisolone). A review by Youssef et al[6] considering the infection risk and safety of corticosteroid use in patients with rheumatic conditions found that for systemic infections, evidence

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from randomized controlled trials (RCTs) showed 'no significant increased risk of infection was noted in the corticosteroid arms in most of the trials', although their review of observational studies found corticosteroid use conferred a dose-related increased risk of infection and the authors recommended an analysis of the risk-benefit ratio; patients with rheumatic conditions are a group whose underlying condition is known to confer approximately double the population baseline risk of developing infections.[7] As the observed increased risk in observational studies was dose-dependent, it is important to distinguish between the very small doses used in most musculoskeletal CSI compared to the doses described in the quoted literature.

The Lancet papers of both Huang[8] (an observational case series from Wuhan) and Russell[9] (a commentary published in the same edition of The Lancet) both relate to therapeutic use of systemic corticosteroid in the treatment of patients hospitalized with COVID-19 infection, and so are not of direct relevance to single-dose peripheral CSI in asymptomatic patients for the management of musculoskeletal pathology; the papers recommended against systemic use of corticosteroids in the treatment of established COVID-19 infection. Other authors however have systematically reviewed the available evidence regarding treatment with immune-supressive and stimulating drugs and COVID-19 infection and concluded that despite the interim World Heath Organization (WHO) advice against therapeutic use of corticosteroids in the treatment of COVID-19 infections, there was evidence that "low-dose prednisolone (and tacrolimus) therapy may have beneficial impacts on the course of SARS-CoV-2", although noting that this observation was not specific for COVID-19, and the observation required further validation.[10] In any event, the systemic effect of peripheral CSI upon endogenous cortisol pathways is relatively short-lived; Habib[11] found the systemic effect of CSI on endogenous cortisol appears to be maximal after 48 hours and to last for one to four weeks.

The potential for CSI increasing susceptibility to viral infection was drawn from the 2018 Sytsma et al[12] study, which considered the potential influence of CSI on the subsequent risk of contracting influenza; the retrospective study found on multivariate analysis that CSI was the most important predictive factor for contracting influenza, with overall rates of observed influenza infection over the five year period considered of 1.08% in the 43,236 vaccinated control patients, 1.64% in 15,018 vaccinated patients who also had at least one CSI, and 1.70% in 4,804 unvaccinated patients who received at least one CSI; this represents an absolute increase in annual infection risk of only around one in 1,000. The mean dose-equivalent of methylprednisolone administered with each CSI was 65.9 mg (over x1.5 the standard dose administered with single site injections in the hand and upper limb). Unfortunately, the paper did not report the timeline of events (CSI-immunization-infection), which in light of the time course of adrenal suppression noted above would have been important to know when interpreting the relevance of the observed differences.

British clinicians are practicing in an environment where they feel that they would be subject to reproach in the event that they should consider CSI for their patients. Other developed countries have not proceeded down the road of strongly recommending against CSI in the management of patients with musculoskeletal problems despite the pandemic; the only national guidance issued in the USA was a joint statement from the American Society of Regional Anaesthesia and Pain Medicine and the European Society of Regional Anaesthesia & Pain Therapy,[13] which noted the implications of CSI in terms of influenza risk and immune suppression, and advocated that clinicians should "consider evaluating risks/benefits of steroid injections and use a decreased dose, especially in high-risk patient populations". The Australasian Musculoskeletal Imaging Group (AMSIG) issued a response to the recommendations from the BSSR in a bulletin headlined "AMSIG recommends that members continue to perform image-guided corticosteroid injections during the COVID-19 pandemic where they are clinically indicated following informed consent" and noting that the BSSR statement had not in fact advocated complete cessation of CSI despite the C19 pandemic.[14] Of additional note, the Allergic Rhinitis and its Impact on Asthma-European Academy of Allergic and Clinical Immunology (ARIA-EAACI) joint statement has recommended that intra-nasal corticosteroid use should not be stopped even in patients with C19, stating that suppression of the immune system had not been proven and that sneezing could disseminate the virus,[15] despite the evidence of a small (4.2%) risk of cortisol suppression from intranasal steroid cited in the systematic review of Broersen et al.[16]

On first review, the current UK guidance has been interpreted as being of direct relevance to the present COVID-19 pandemic, and in light of the wording of the documents (indicating that risks apply to asymptomatic individuals who may be incubating COVID-19 (i.e. potentially all people, given the high community prevalence of COVID-19)[4] as representing an absolute or at least a strong contraindication to administration of even low dose CSI. However, our review of the various documents show that they do not in fact advocate the complete cessation of CSI, but that prior to proceeding with CSI, clinicians should think about and discuss the potential risks and benefits of the CSI to their patients. In the NHS England document of 25 March they recommend 'only consider steroids if patient has high levels of pain and disability, has failed first-line measures and continuation

of those symptoms will have a significant negative effect on their health and wellbeing';[3] we consider this advice reflects a position where, with appropriate caution and thought, CSI can continue to be offered to patients.

When faced with uncertainty, it is understandable to remain circumspect. While the guidelines have not advocated an embargo on CSI, it appears that many practitioners and providers are reluctant to consider CSI as a treatment option during this pandemic. Such approach would deny patients a treatment that could alleviate pain and improve quality of life. In the current climate where the timing of reinstatement of elective surgery remains indeterminate, judicious use of CSI for many patients would delay, if not remove, their need for surgery.

While considering and exploring non-interventional treatments and, in the event that none are acceptable or effective, minimizing the total dosage of corticosteroid administered in the event of injections being requested seems sensible, nevertheless removing CSI as a legitimate treatment option does not seem to be a measured or responsible medium-to-long term choice for the good of a sizable cohort of patients. Musculoskeletal conditions represented a substantial primary care burden, prompting approximately one in four attendances,[17,18] only a proportion of which reach secondary care, given the prevalence of carpal tunnel syndrome (7% to 16%),[19] trigger finger (~ 3%)[20] and thumb-base arthritis (1.4% overall, > 5% in women aged 70 to 74 years)[21] to mention only a few of the hand conditions commonly treated by CSI, which is a treatment widely used in many other musculoskeletal conditions. Minimally-invasive treatments, such as CSI, have long played an important role in addressing patients' symptoms without the need to revert to hospital attendances, a role that is particularly important in the current viral climate to stop potentially vulnerable patients from needing to attend hospitals, or to need to be considered for surgery.

A reassessment of the existing guidance and a balanced consideration of the evidence, avoiding any unintended inhibiting effects of interpretation is required. We think it is important that practice accurately reflects the content of the current guidelines on the use of CSI. Where a patient has significant disease activity and there are no effective alternatives, CSI should be considered following a shared risk assessment with the patient as part of 'Montgomery guided' consent process.

With careful shared decision-making, recognizing the potential but, in all probability, very low risks of CSI in the setting of COVID-19, and after appropriate patient selection and counselling, we feel continued use of CSI in low doses remains an appropriate treatment option for many patients.

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- C. Y. Ng: Wrote and reviewed the manuscript.
- D. Warwick: Reviewed and edited the manuscript.

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