Steroid injections in musculoskeletal conditions and COVID infection rates: what is the impact on positive rates following the injection?

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Abstract

Background and aim

Therapeutic glucocorticosteroid injections are commonly utilised to manage musculoskeletal complaints. Following the SARS-CoV-2 pandemic, national guidelines advised against their use due to potential immunosuppressant effects. The aim of the study was to determine whether steroid injections for musculoskeletal conditions impacts on positive COVID 19 infection rates.

Patients and Methods

This retrospective evaluation involved primary care participants who received a steroid injection for a musculoskeletal condition. 291 participants receiving a total of 299 steroid injections entered the study between the 25th September 2020 and the 29th April 2021.

Results

6 participants had positive PCR tests, averaging 22.83 days (SD 10.48) after the injection. An infection rate of 2.06% was demonstrated in the injection group with the control group demonstrating 6.97% (p=0.000752) with statistical significance set at P=0.05. The odds ratio was identified as 0.27 indicating a lower odds of a positive PCR test compared with the control group.

Conclusions

This retrospective evaluation found a low risk of positive PCR tests for low and moderate COVID-19 risk patients injected during the COVID-19 pandemic. Glucocorticosteroid injections within the COVID-19 pandemic were not associated with higher COVID-19 rates compared to the local population, in fact, they were related to lower rates. For future studies, large scale studies and meta analyses are needed to provide greater generalisation to the population.

Introduction

In December 2019 an atypical severe acute respiratory syndrome occurred within Wuhan, China and rapidly spread throughout the world creating a Worldwide Pandemic. The disease referred to as COVID-19 was caused by a novel coronavirus known as SARS-CoV-2. The SARS-CoV-2 infection can trigger both innate and adaptive human immune system responses which if uncontrolled can lead to local and systemic tissue damage (Cao, 2020). The virus can activate immune responses and trigger significant antibody production along with significantly elevating pro-inflammatory cytokines levels (Cao, 2020). Various symptoms are recognised in response to COVID-19 infection and these are predominantly respiratory system symptoms but can affect multiorgan systems and have led to significant fatalities (Yuki et al, 2020). In January 2020 the first positive COVID-19 case was found in the United Kingdom causing significant impact on a wide spectrum of services, none the least the NHS. By March 2020 a National Lockdown was introduced and people were told to work from home and not travel unless absolutely necessary. As a result, face to face clinics within Musculoskeletal (MSK) Physiotherapy services including injection clinics, were ceased.

Musculoskeletal condition management in Physiotherapy, Orthopaedic and Rheumatological services utilise glucocorticosteroid injections (CSIs) as adjuncts to help manage multiple musculoskeletal and inflammatory disorders. Glucocorticosteroids play vital roles in maintaining homeostasis and influencing innate immune responses and are recognised as providing both anti-inflammatory and pro-inflammatory responses through influencing glucocorticoid receptors via various mechanisms (Cruz-Topete & Cidlowski, 2015). They provide their anti-inflammatory effect by reducing inflammatory mediator production and release, causing vascular reaction suppression that occurs during the inflammatory response (Becker, 2013). The immunosuppressant effects predominantly occur through their effect on

the hypothalamic-pituitary adrenal axis (HPA) and their inhibitory effects on macrophages and T cells as well as leucocyte function (Becker, 2013). Inflammation is common within musculoskeletal conditions therefore glucocorticosteroids are potent anti-inflammatories that are routinely administered in MSK practice to reduce inflammation, manage pain and improve function (Stephens et al, 2008).

Following the pandemic outbreak various societies (Faculty of Pain Medicine of the Royal College of anaesthetists, 2020, British Society of Skeletal Radiology, 2020, British Society of Rheumatology, 2020, British Pain Society, 2020) produced National guidelines regarding CSI use due to their immunosuppressant effects and subsequent potential increased risk of developing COVID-19. These guidelines clearly highlight that injections should only be considered with severe disease activity or with significant levels of pain and disability and in cases with no alternative treatments (BSR, BOA, BASS, RCGP, BSIR, FPM, BPS, CSP, 2020). Further guidance advocated against injection therapy for vulnerable patient groups, that is, those over the age of 70 with co-morbidities such as diabetes, ischaemic heart disease or chronic respiratory disorders as they are classified as high risk of developing COVID-19 (BSR, BOA, BASS, RCGP, BSIR, FPM, BPS, CSP, 2020).

Within the current study the most commonly utilised glucocortiocosteroid for managing musculoskeletal complaints was Triamcinolone Acetonide and this study utilised this drug solely. Triamcinolone Acetonide has been demonstrated to cause adrenal suppression within the first 48 hours following administration (Fascia et al, 2020) with these effects continuing for 30-40 days (Fascia et al, 2020, Broersen et al, 2015). Broersen et al (2015) found that adrenal suppression with the use of corticosteroids has been particularly apparent following administration of an intra-articular joint injection with 52% of patients developing adrenal insufficiency following joint injection. With the recognised immunosuppressant effects, it remains unclear the potential impact that this suppression may have and whether it leads to

increased coronavirus infection at the time of injection, or within the proceeding 40 days (BSR, BOA, BASS, RCGP, BSIR, FPM, BPS, CSP, 2020).

This evaluation, therefore, aimed to ascertain whether any significant risk was apparent providing evidence for, or against, the use of corticosteroid injections during such pandemic situations, providing useful evidence to aid in shared decision making with regards to administering CSIs.

Aims:

1. Steroid injections in musculoskeletal conditions and COVID infection rates: What is the impact on positive rates following the injection?

2. To determine whether COVID 19 positive results differed between risk category (mild or moderate)

3. To determine whether there was any relationship between steroid dose and those demonstrating a positive PCR test for COVID-19 following a CSI

Research Design & Methods

The evaluation utilised data routinely gathered by a Healthcare organisation. A report containing a list of patients injected within the service between 25th September 2020 and 29th April 2021 was obtained. This timeframe was chosen as the start date was recommencing injection therapy within the Healthcare organisation following the original cessation at the start of the pandemic and the end date was via convenience sampling as it was the latest date

available at the time of data collection, which provided the greatest number of potential participants.

Each participant was given a reference number which was recorded along with data on injection date, body part injected, dose and patient demographics.

The control group was obtained through data provided by the Office of National Statistics (2020) which provided daily COVID-19 case numbers for the Hull region within the United Kingdom, for the duration of the data collection period. This provided accurate daily cases and up to date population data that was used to calculate the average number of positive COVID-19 cases within the Hull region. The control and intervention groups were both obtained from the Hull region making the groups more reflective of each other and allowing direct comparison of COVID-19 levels.

A review of the patient records within the General Practice database was performed by the author to obtain records of any positive polymerase chain reaction (PCR) COVID-19 tests within a 40-day period following corticosteroid injection. Further data regarding the COVID-19 risk group of each patient was obtained and was based around the NHS risk criteria (NHS Digital, 2021). Positive COVID-19 PCR test data was recorded alongside the date of the positive test, the number of days elapsed between the positive test and the injection and the who had a positive COVID-19 test following injection.

Participants

National guidelines and company policy during the Pandemic meant that participants were excluded from injection if they were considered high risk of COVID-19 development as per the NHS risk category (NHS Digital, 2021) or were under the age of 18 years. The study utilised low and moderate COVID 19 risk patients indicating that they were systemically well

without any significant past medical history (including active inflammatory arthropathies) and were not taking immunosuppressant medication. The vast majority of the subjects were injected into a single joint / soft tissue and other than the presenting musculoskeletal condition were otherwise fit and healthy. Retrospective convenience sampling was used to obtain the participants as its emphasis was based on a known population of people injected within the MSK service and could not, therefore, be truly random. The sample size was determined via convenience sampling as it encompassed the greatest number of participants available at the time of data collection.

Findings / Results

Between 25th September 2020 and 29th April 2021 (216 days), 575 triamcinolone steroid injections were administered to a total of 560 patients. Unfortunately, due to a lack of General Practice data sharing, access to full patient records was only available for 291 participants receiving a total of 299 steroid injections. Of the 291 participants 183 were female (62.89%) and 108 were male (37.11%) with an average age of 59.73 years (range 33-88 years, standard deviation 11.15). Within the injection group, 184 participants (63.2%) were in the low risk of COVID-19 development group and 107 (36.8%) in the moderate risk group.

Various soft tissue and joint injections were administered for multiple musculoskeletal complaints during the evaluation period with varying doses of triamcinolone acetonide used with an average dose per injection of 19.44mg (range 10-40mg, SD 12.11). The steroids were injected independently or diluted with either lidocaine hydrochloride 1 or 2% or sodium chloride 0.9%. in the most frequently injected sites were the shoulder (23.1%) and knee joints (22.1%) making up 45.2% of the total injections with a mean dose of 40mg of triamcinolone acetonide per injection. Of the 299 injections 150 (50.2%) were performed under ultrasound

guidance and 149 (49.8%) were blind injections. The site and injection doses utilised are listed in Table 1.

Site of injection	Number of injections	Steroid dose in mg
Acromioclavicular Joint	8	10
Carpal Tunnel	13	20
Carpometacarpal Joint	15	10
De Quervain's Tenosynovitis	5	10
Elbow Joint	2	10
First Metatarsal Joint	2	20
Foot Injection	1	10
Greater Trochanteric Pain	8	20-40
Golfers Elbow	2	10
Hip Joint	17	40
Knee Joint	66	40
Lateral Coronary Ligament Knee	1	40
Morton's Neuroma	9	20
Plantar Fascia Injection	12	15-20
Shoulder Joint	69	40
Subacromial Bursa	39	20
Tarsometatarsal Joint	6	20
Tennis Elbow	7	10

Trigger Finger / Thumb	16	10
Wrist Joint	1	10
		Mean Dose: 19.44
		Range 10-40

Table 1. Site and dose of Triamcinolone Acetonide injection

The control group contained 259,481 participants, which was the regional population and over the study duration 18,088 participants recorded positive PCR tests[12] (absolute risk = 6.97%) of the regional population testing positive for COVID-19.

The General Practice database for each participant who had received a steroid injection was reviewed for positive PCR COVID-19 tests within 40-days of the injection. 6 participants (absolute risk = 2.06%) were identified as having a positive PCR test within 40-days with 4 being male and 2 being female (Figure 1). The number need to treat was calculated as 20.12.

Insert figure 1 here

Figure 1. Timeline of the number of days passed between glucocorticosteroid injection, positive COVID 19 test and the COVID 19 risk category

The average age of these participants was 56.83 years (range 45-63 years, SD 6.85). 5 out of the 6 participants (83.33%) were in the low COVID-19 risk group and 1 participant (16.67%) was in the moderate COVID-19 risk group (Figure 1). The injection sites varied in location within this group with 2 participants (33.33%) receiving shoulder joint injections and the remaining 4 receiving injections into different soft tissues and joints (Table 3). Ultrasound guidance was used to perform 4 (66.67%) out of the 6 injections with 2 (33.33%) performed blind. The average dose of triamcinolone acetonide injected was 28.33mg (range 20-40mg,

SD 9.83) per injection for this group and each injection with the exception of 1 was diluted with lidocaine hydrochloride 1 or 2% ranging from 1-9ml.

Injection Site	Number	Dose of Steroid	USGI Or Blind
Subacromial Bursa	1	20	USGI
Carpal Tunnel	1	20	Blind
Plantar Fascia	1	20	Blind
Shoulder Joint	2	30/40	USGI (x2)
Hip Joint	1	40	USGI

Table 2. Intervention group positive COVID-19 participant injection sites. USGI = Ultrasound guided injection

The average time that elapsed between the injection and positive PCR COVID-19 test was 22.83 days (range 7-33 days, SD 10.48). 4 (66.67%) out of 6 participants received their injection when case numbers were relatively low and the remaining 2 (33.33%) received their injection during the peak of positive PCR tests when the infection rate was at its highest within the study period (Figure 2).

Insert figure 2 here

Figure 2. Date of confirmed COVID-19 cases in North of England Region also indicating date steroid injections were administered for positive COVID-19 participants

The Fisher's exact test demonstrated a p-value of less than 0.05 (p=0.0002) with an odds ratio of 0.27 (Table 3).

	Positive COVID-19 PCR test	**Negative or no COVID-19 PCR test**	**Total**	**Odds**
CSI Positive PCR test group	6	293	299	0.02
Control Group	18088	241393	259481	0.07
Total	18094	241686		
Results	Odds Ratio = 0.27		259780 (Grand Total)	
	Fisher's exact test p=0.0002			

Table 3. Odds ratios and Fisher's exact test results

Discussion

At the start of the COVID-19 pandemic there was significant concern over the potential immunosuppressant effects and subsequent COVID-19 risk posed following corticosteroid therapy. This study demonstrates a low incidence within the UK based cohort of a positive COVID-19 PCR test following a corticosteroid injection for a musculoskeletal complaint. There were only 6 positive PCR tests out of 299 injections with an infection rate of 2.06% which when compared with the infection rate of 6.97% positive COVID-19 tests within the control group. The Fisher's exact test demonstrated a p-value of less than 0.05 (p=0.0002) indicating dependent variables given the statistically significant difference between those injected and the control group. The odds ratio was 0.27, which being less than 1 indicates that the exposure (CSI) was associated with lower odds of the tested outcome (positive PCR test for COVID-19) when compared with the control group. This highlights that injection of triamcinolone acetonide was a low risk procedure for patients within the low and moderate COVID-19 risk groups and interestingly the infection rate was less than that of the local population. This could be due to the potentially beneficial effects of glucocorticosteroids in treating COVID-19 as Finney et al. (2020) demonstrated. They noted a potential reduction in susceptibility of chronic obstructive pulmonary disease (COPD) patients receiving inhaled corticosteroids due to a reduction in SARS-CoV-2 entry receptor ACE2 however given the greater dose, regularity and method of delivery of the inhaled steroid it may be feasible that this reduction in infection rate may well have occurred due to other causes. Extensive

counselling and written consent process including the discussion of the risks and benefits of the CSI prior to receiving the injection may have led to greater caution being shown by the participants and taking more precautions with regards to social contact and self-isolation/distancing and carrying out more effective hand hygiene measures in the knowledge that the steroid can reduce the immune response. The findings of this study are consistent with and in keeping with other studies (Chang et al, 2021, Aziz et al, 2021, Bugeja et al, 2021, Newton et al, 2020, Regan, 2021, Morgan et al 2020, McClean et al, 2020). The risk identified within those studies demonstrated extremely low infection risk with very few or no positive cases of COVID-19 infection following CSI.

Since the initiation of the presented study others have also investigated this topic. One example (Bugeja et al, 2021) carried out a retrospective study on 734 participants who received a CSI for a musculoskeletal complaint and reviewed any subsequent COVID-19 development. The study had chosen a 30-day timeframe for the action of the steroid which may have limited the number of positive cases highlighted. They found no increased risk of contracting COVID-19 following CSI. The study used an intervention group as well as a matched, randomly selected control group. Appropriate statistical testing using the Fisher's exact test was performed on the data given the relatively low sample size and no statistically significant difference (p-value <0.05) was apparent between the intervention group and control group. 4 participants developed COVID-19 within 30 days with 3 out of the 4 receiving injections into more than one body part. This may indicate that they received a higher dose of corticosteroid than those with single joint/soft tissue injections and subsequently at higher risk of Hypothalamic pituitary adrenal (HPA) axis suppression, as a dose dependent relationship exists with regards to higher doses of glucocorticosteroid leading to greater levels of adrenal suppression (Habib, 2009).

Chang et al. (2021) within their prospective study of 66 patients undergoing image guided corticosteroid injections demonstrated no statistically significant difference in COVID-19

infection rates when compared with the general population. Unfortunately, only low participant numbers were recruited limiting the statistical power of the results (n=66). The study was also carried out during the second part of the lockdown period whereby the rate of COVID-19 infections within the general population would have been low and at that time widespread testing was not available for the general population indicating that a true COVID-19 infection rate for this particular population was unknown. Although limitations were apparent, only one out of 66 participants (1.52%) went on to develop COVID-19, 19 days following their injection with no other patients reporting symptoms or testing positive for COVID-19.

McKean et al (2020) within their retrospective observational study of 504 CSIs reported very low incidences of positive COVID-19 infections following a CSI with no adverse clinical outcomes. Of the 504 injections only 11 COVID-19 tests were performed on 9 patients with no positive results found reinforcing the low risk of the procedure, however the participant numbers were relatively low limiting the determination of any absolute risk. The study referred to Upper Tier Local Authority (UTLA) COVID-19 infection rates as a comparison however no direct control group was used and the infection rates within the UTLA would have included patients within high COVID-19 risk groups. These patients were excluded within this study as the national guidance advised against utilising CSIs for this particular patient group due to the elevated COVID-19 development risk. Therefore, the comparison needs to take into account that this particular infection rate may have varied for their population group. Within both the McKean et al (2020) study and also the present study an element of bias may have been introduced as they were based on specific local populations with unique demographics in terms of socioeconomic group and race. The national guidance on informed consent prior to CSI and the requirement to explain in depth the potential risk may also have influenced the participants leading them to self-isolate and demonstrate greater COVID-19 precautions than those within

the general population potentially affecting the risk posed due to the reduced contact with COVID-19.

Since the onset of the COVID-19 pandemic several studies (Yu et al., 2021; RECOVERY Collaborative Group, 2021) have been published relating to the treatment of COVID-19 with oral, inhaled and intravenously administered glucocorticoids. The PRINCIPLE study (Yu et al., 2021) in their randomised controlled trial of 4,700 participants utilised inhaled budesonide in the treatment of COVID-19 patients and compared this to usual care and usual care with an alternative treatment and found improvement in time to recovery in higher risk complication groups receiving this therapy compared to those who did not however the probability to superiority was below the threshold specified. Further support for corticosteroids in the treatment of COVID-19 was found within The RECOVERY trial RECOVERY Collaborative Group, 2021) in their randomised controlled trial of 9355 participants who compared patients receiving dexamethasone with usual care for hospitalised patients with COVID-19 and found a reduced 28-day mortality rate with oral or intravenous dexamethasone in COVID-19 patients receiving oxygen therapy and mechanical ventilation and this has since been recommended as treatment for these patients via NHS England (2020).

Limitations

There are several limitations to this study starting primarily with relatively low participants numbers which unfortunately was compounded by the lack of General Practice data sharing which significantly reduced total participant numbers. There was potential risk of bias given the very specific local participant demographics used in terms of ethnicity and socioeconomic group making it more difficult to generalise the findings to the general population.

This evaluation relied on accurate COVID-19 testing in the form of PCR tests and these have a pre-test probability of 80%, a sensitivity of 70% and a specificity of 95% (Watson et al.,

2020) leading to understandable false positives and false negatives in the testing. As well as accepting the lack of total accuracy of the testing, reliance upon patients actually attending for swab testing when they had symptoms was also a potential limitation however it is hoped this was consistent between both groups. Furthermore, not all participants were tested for COVID-19, leaving the potential that some injected participants may have developed COVID-19 but were asymptomatic given that a high proportion ranging from 20-75% of COVID-19 infections are asymptomatic (Yanes-Lane et al., 2020).

The control group included participants that tested positive for COVID-19 and may have been in the high risk of developing COVID-19 category and these were excluded from this study, which may have influenced the infection rate within the local population. The data utilised for the control group may also have included positive lateral flow tests as the PCR testing was usually carried out following a positive lateral flow test and, therefore, some of the positive COVID-19 cases may have been awaiting PCR tests. Unfortunately, it is feasible that some of the participants within the intervention group may have had positive tests in different regions within the UK and that these may not have been recorded in their General Practice patient notes, however England had its second and third national lockdowns during the study period with various restrictions placed upon general movement, therefore, it is hoped that any missing data would be negligible. Given the nature of the consent process and guidelines put in place during the pandemic, even greater emphasis was placed on explicitly detailing the risks of the CSI making very specific reference to the immunosuppressant effects and the subsequent risk of developing COVID-19 with written consent being gained prior to the procedure. Telephone consultations prior to the CSI were carried out informing the patient of the risks and advising self-isolation and social distancing following the CSI which may have resulted in the participants demonstrating greater levels of distancing from society in fear of developing COVID-19. The timeframe utilised within the study was set at 40 days as several studies

(Fascia et al, 2020, Broersen et al, 2015) had highlighted a 30-40 day duration of steroid action therefore the highest reported duration of action of the steroid was utilised.

Conclusion

This retrospective evaluation found a low risk of a positive PCR test for COVID-19 for participants within low and moderate COVID-19 risk categories, injected with triamcinolone acetonide for a musculoskeletal complaint. None of the participants that tested positive for COVID-19 following a CSI had had a vaccination prior to their injection leading to reinforcement that the procedure appears to be low risk. The COVID-19 infection risk within the control group was greater than those receiving a CSI, providing confirmation that CSI for this patient group was low risk. The study demonstrates that there was no greater risk of a positive COVID-19 PCR test with increasing doses of triamcinolone acetonide and there was no evidence of any increased risk whether the injection undertaken was targeted at soft tissue or administered within local joints. A very small increased rate of positive PCR tests were associated with those injected under ultrasound guidance, however, the participant numbers were too low to draw any significant conclusions. There was no evidence that increasing age increased the risk of positive PCR tests following CSI or that participants within the moderate risk of developing COVID-19 categories were at greater risk of positive PCR results. There was a slight increased rate of a positive PCR test in males with a greater number of participants testing positive following a CSI but the low numbers prevent inference about gender differences.

The findings of this study add to the current base of literature concerning the low risk of utilising CSI injection therapy during the COVID-19 pandemic. All of the patients that were

injected and subsequently went on to have a positive PCR test did not appear to experience severe symptoms as none were admitted to hospital. This study agrees with the national guidelines in that there is a risk of developing COVID-19 following a CSI however that risk in the studied population is low. Caution should be taken when considering CSI as a treatment option with a thorough risk/benefit analysis considered. Greater emphasis on shared decision making should be carried out with alternatives discussed prior to contemplating CSI to minimise the risk posed but there does not appear to be an increased risk of contracting COVID due to a CSI using Triamcinolone Acetonide for routine MSK conditions.

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