Radiology

The Relationship of Imaging-guided Corticosteroid Injections to COVID-19 Incidence in the Pandemic Recovery Period

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Summary statement: Participants who received imaging-guided corticosteroid injections for pain management during the COVID-19 recovery period did not have an increased incidence of COVID-19 compared with the general population.

Key Results:

- In a prospective study of 1960 adults undergoing image-guided corticosteroid injections for pain management during the COVID-19 pandemic, the rate of symptomatic COVID-19 within 28 days was lower than that of the state population (0.5% vs 7.5%, respectively, $p < 0.001$)
- At up to 4 months after injection, the rate of symptomatic infection (2.2%) was also lower than that of the general population ($p < .001$).

Abbreviations:

BMI – body mass index

RT-PCR – reverse transcription-polymerase chain reaction

Abstract

Background: Corticosteroids injected for the treatment of musculoskeletal pain are systemically absorbed and can affect the immune response to viral infections.

Purpose: To determine the incidence of symptomatic COVID-19 disease in individuals receiving image-guided corticosteroid injections for musculoskeletal pain compared with the general population during the pandemic recovery period.

Materials and Methods: In this prospective cohort multicenter study, adults with a history of musculoskeletal pain who underwent imaging-guided intra-articular and spine corticosteroid injections between April 2020 and February 2021 were consecutively enrolled. Participants were followed for a minimum of 28 days through their electronic medical record (EMR) or by direct phone call to screen for COVID-19 test results or symptoms. Clinical data including body mass index (BMI) was also obtained from the EMR. Incidence of COVID-19 in the state was obtained using the Massachusetts COVID-19 Response Reporting website. Student t tests were used for continuous variable comparisons. Univariable analyses were performed using Fisher exact tests.

Results: A total of 2714 corticosteroid injections were performed for 2190 adult participants (mean age ± standard deviation, 59 ± 15 years, 1031 women). Follow-up was available for 1960 (89%) participants who received 2484 injections. Follow-up occurred 97 ± 33 days (range 28 – 141 days) after the injection. There were 10/1960 participants with COVID-19 within 28 days from the injection (0.5%, 95% CI, 0.24-0.94%) and 43/1960 participants with COVID-19 up to 4 months after the injection (2.2% 95%CI, 1.6-2.9%). This was lower than the incidence rate in the population of Massachusetts during the same period (519,195/6,892,503, 7.5%, P <.001 both at 28 days and 4 months). Participants diagnosed with COVID-19 (n=10) at 28 days had higher BMI than the entire cohort (n=1960) (32 ± 10 vs. 28 ± 6 kg/m^2, P=.04).

Conclusion: Adults who received image-guided corticosteroid injections for pain management performed during the pandemic recovery period had a lower incidence of symptomatic COVID-19 compared with the general population.

Introduction

Corticosteroid injections are a first-line treatment for musculoskeletal pain (1–3). During the beginning of the COVID-19 pandemic, concerns about the safety of intra-articular and spine corticosteroid injections were raised due to known systemic absorption and effects on the immune system (4,5). Corticosteroids have direct effects on immune cells, including a reduction in the ability of neutrophils to migrate to sites of infection, impairment of macrophage and monocyte function, and suppression of the hypothalamus-pituitary-adrenal (HPA) axis (5–7). When the HPA axis is suppressed by exogenous steroids via negative feedback, the organism becomes more vulnerable to the effects of the inflammatory cascade that happens in response to a pathogen such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (7,8). After an intra-articular or spine corticosteroid injection, HPA axis suppression usually peaks at 24 –48 hours and may take up to 4 weeks for normalization (4,9–13). In a meta-analysis by Broersen et al, adrenal insufficiency was seen in up to 52.2% of subjects after intra-articular corticosteroid injection (14).

Corticosteroid hesitancy also derived from epidemics of other viruses, including influenza, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS), in which critically ill individuals receiving systemic corticosteroids showed worse outcomes than the general population (15–17). Due to the initial uncertainty, professional societies issued statements advising against elective corticosteroid injections, leading to disruptions of musculoskeletal pain treatment services throughout the world (18–21). In February 2021, the American Academy of Orthopedic Surgeons (AAOS) recommended that alternative options to corticosteroids should be considered for treatment of musculoskeletal pain and that

patients should be counselled regarding potential immunosuppression risk associated with corticosteroids (22).

The results of studies evaluating individuals who received injections during the lockdown period have been reassuring, but the changes in public health policies, including decreased physical distancing and the reopening of businesses, and potentially higher exposure when vaccines were not yet available, warrant additional investigation about the safety profile of corticosteroid injections during the COVID-19 pandemic (19,23–26).

The purpose of our study was to determine the incidence of symptomatic COVID-19 disease in individuals receiving fluoroscopic and US-guided corticosteroid injections for musculoskeletal pain compared with the general population during the recovery period of the COVID-19 pandemic.

Materials and Methods

The authors declare no conflict of interest. The population analyzed in this study partially overlaps with that used in a previous study (23). However, the analysis on the current study includes additional data from an extended follow-up period, and offers a more robust evaluation of the relationship between corticosteroid injections and incidence of COVID-19. This prospective study was HIPAA compliant and institutional review board approved, with verbal consent of the participants for participation.

Participant Selection

Inclusion criteria were: (1) adults (age above 18 years) (2) with a history of musculoskeletal pain who were scheduled for image-guided corticosteroid injection at our

primary large academic center or affiliated community hospital. A convenience sample of participants who received injections from April 15, 2020, through February 26, 2021 was used. The exclusion criteria were: (1) age equal to or below 18 years; (2) pregnancy; (3) procedures in which corticosteroids were not administered; (4) aborted procedures; and (5) participants lost to follow-up. The follow-up period included the last few weeks of the lockdown period in the state of Massachusetts (4/15/2020 – 5/18/2020) and the different recovery phases that were part of an official government plan for reopening businesses and industries in the state: Phase I (5/19/2020 – 6/7/2020), Phase 2 (6/8/2020 – 7/12/2020), Phase 3 step 1 (7/13/2020 – 10/4/2020), Phase 3 step 2 (10/5/2020 – 12/13/2020), and rollback to Phase 3 step 1 (12/14/2020 – 02/26/2021). The COVID-19 vaccine rollout in the state started on 12/15/2020, initially targeting healthcare workers and first responders only. General public vaccination began on 2/1/2021 for people ≥ 75 years old, and on 4/19/2021 for those ≥ 16 years old. The state government of Massachusetts provides publicly available information on COVID-19 cases in the state through their COVID-19 Response Reporting website. (27).

Image-guided corticosteroid injections

Injections were performed by a fellowship-trained musculoskeletal radiologist or by musculoskeletal radiology fellows or a radiology assistant with 8 years of procedure experience and supervised by musculoskeletal radiologists with < 5 years (J.R.T.V., M.J., R.R.B.), 5-10 years (A.B.K., J.S.H., F.J.S., C.Y.C.) and >10 years (M.A.B., A.J.H., W.E.P) of experience. Extra measures in scheduling and preprocedural practices to physically distance participants and to minimize waiting room time were in place during the entire study period with minimal changes throughout the year according to hospital policy. All participants were called the day

before the exam to screen for sick contacts or symptoms of COVID-19. From April through June 2020, participants were instructed to physically distance for 1-2 weeks after the injection. This formal recommendation was later discontinued although general safety measures were still endorsed for the remainder of the study period.

Injections were performed under a sterile technique, which included the use of povidone-iodine or chlorhexidine for puncture site cleaning. Radiologists and technologists wore personal protective equipment per hospital policy, including surgical masks and eye protection or face shields. Fluoroscopic or US guidance was used. Iodinated contrast (Omnipaque, 300 mg I/mL, GE Healthcare) was used for the confirmation of needle location for the injections performed under fluoroscopy.

The following corticosteroids and doses were used: betamethasone sodium phosphate and acetate injectable suspension (6 mg/mL, American Regent Inc.; 6–21 mg), Kenalog (triamcinolone acetonide injectable suspension 40 mg/mL, Bristol Myers Squibb Company; 40–160 mg), Depo-Medrol (methylprednisolone acetate 40 mg/mL, Pfizer; 60-80 mg), or dexamethasone (4 mg/mL, Fresenius Kabi; 10 mg). Injections were performed with and without anesthetic, which included lidocaine 1% (AuroMedics Pharma LLC; 1–4 mL), ropivacaine 0.2% (AuroMedics Pharma LLC,; 1–5 mL) or bupivacaine 0.5% (Hospira, Inc.; 2– 4 mL).

Postprocedure survey

At least 1 month (28 days) following the injection, electronic medical records (EMRs) were reviewed for hospitalizations, emergency room or clinic visits for COVID-19 symptoms, and SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) tests. If no records were available, participants were contacted via direct phone call. The investigators were

responsible for reviewing EMR data (J.R.T.V., CYC, and S.H.) and for the follow-up phone calls (J.R.T.V., A.B.K., F.J.S. and C.Y.C.). Participants were considered lost to follow-up if (1) there was no clinical information available in the EMR at least 1 month (28 days) after the procedure AND (2) they could not be reached by phone after two attempts on different dates.

The criteria for a positive COVID-19 case following corticosteroid injection were: (1) EMR documentation of new symptoms concerning COVID-19, in conjunction with a positive RT-PCR test within 28 days from the injection, (2) EMR documentation of a positive RT-PCR test within 28 days from the injection, or (3) confirmation via phone call of the development of symptoms with a subsequent clinical diagnosis of COVID-19 and/or positive RT-PCR test within 28 days from the injection. The cutoff of 28 days was chosen due to data from studies showing that corticosteroid effects on the HPA axis and immune system can persist for up to 4 weeks. (28). Additional positive cases up to 4 months were documented and analyzed separately.

Criteria for a negative COVID-19 case were: (1) no symptoms concerning COVID-19 at least 1 month (28 days) and up to 4 months from the injection, with or without a negative RT-PCR test, or (2) no documentation of in-person visits to the hospital at least 1 month (28 days) and up to 4 months after the injection. All participants with in-person appointments at both participating hospitals were screened for symptoms, a history of COVID-19 and sick contacts using a standardized questionnaire during the entire study period (Figure E1 in Appendix E1). The clinical notes were also used to confirm the absence of symptoms or COVID-19 diagnosis since the date of the injection.

Additional information obtained from the EMRs included the laterality and type of injections, body mass index (BMI, kg/m^2) and presence of comorbidities including hypertension, diabetes and an immunocompromised state. Criteria for immunosuppression were: (1) chronic

use of immunosuppressant medications for any indication including inflammatory arthropathy and prior transplant, (2) diagnosis of primary or metastatic malignancy within the past year, (3) chronic kidney disease.

Statistical Analysis

Categorical data are presented as frequencies and percentages, and continuous data are presented using means and standard deviations. For the participants who had two or more visits, the demographic data were based on the clinical information at the time of the last visit. The clinical characteristics of the participants with positive cases were compared with those of the entire study cohort. Student t tests were used for continuous variable comparisons. Univariable analyses were performed using Fisher exact tests (Stata version 16.0, StataCorp LLC,). A two-tailed Bonferroni-adjusted $P < .017$ (0.05/3) was considered statistically significant to account for multiple comparisons and reduce the risk of false-positive results due to multiplicity.

Results

Participant characteristics

A total of 3241 fluoroscopic and US-guided injections for musculoskeletal pain were performed between 4/15/2020 and 2/26/2021, with 527 exclusions due to age ≤ 18 years, injections without corticosteroids (including arthrograms), and aborted procedures. The study cohort included 2714 corticosteroid injections performed for 2190 participants. Follow-up was available for 1960 (1960/2190, 89%) participants (2484 injections), 1450 (1450/1960, 74%) by EMRs only, and 510 (510/1960, 26%) by phone call and EMRs, occurring 97 ± 33 (28–141)

days after the injection (Figure 1). There were 1031 (1031/1960, 53%) women and 929 (929/1960, 47%) men with a mean age of 59 ± 15 years for all participants. A total of 277 participants had two or more visits for injections. The average time interval between injections was 100 ± 65 (1–294) days.

During the entire study period, 10/1960 (0.5%, 95% CI, 0.24-0.94%) participants were diagnosed with COVID-19 within 28 days of an injection. The RT-PCR tests were performed 12 ± 8 (1-22) days after their appointment. These ten participants had a higher BMI than the entire study cohort (32 ± 10 vs 28 ± 6 kg/m^2; P=.04). No differences in other clinical features were seen in this group when compared with the entire study cohort, including the presence of immunosuppression (2/10, 20% vs 141/1960, 7%; P=.14). When considering the period up to 4 months from the injection, 43/1960 (2.2% 95%CI, 1.6-2.9%) participants were diagnosed with COVID-19 were identified. BMI values were also higher for this group (31 ± 7 vs 28 ± 6 kg/m^2; P=.005). Demographics for the entire study cohort and for the participants with positive diagnoses are listed in Table 1. The types of injections and corticosteroid doses are listed in Table 2. The most common symptoms are listed in Table E1 in Appendix E1.

The only positive COVID-19 diagnosis requiring hospitalization was a 72-year-old man with a BMI of 37 kg/m^2 who was admitted due to worsening shortness of breath and found to have COVID-19 and bilateral pulmonary embolism. Patient was treated with anticoagulation and non-invasive ventilatory support and discharged after 12 days without major complications. No COVID-19-related deaths were registered among the participants during the follow-up period. The death of an 87-year-old male participant with diabetes who was diagnosed with a urinary tract infection 9 days after a hip injection was the only registered death in the study cohort.

COVID-19 incidence rates in adults after corticosteroid injection versus the general population

The standardized questionnaire used for the follow-up phone calls is depicted in Figure 2. From April 15, 2020, to February 26, 2021, 519,195 new diagnoses of COVID-19 were registered on the Massachusetts COVID-19 Response Reporting website, with an incidence rate of 7.5% (519,195/6,892,503). Thus, the incidence rate of COVID-19 in the study sample at 28 days from the injection (10/1960, 0.5%; P <.001) and at 4 months after the injection (43/1960, 2.2%; P <.001) was lower than that in the general population. When comparisons were performed for each phase of recovery in the state of Massachusetts, no difference was seen between the number of infections diagnosed up to 28 days from the injections and the new diagnoses in the general population. The only exception was during the rollback to Phase 3 recovery, step 1 (12/14/20 – 2/26/21), in which the rate of infection in the study group (5/576, 0.9%) was lower than that in the general population (267,784/6,892,503, 3.9%; P <.001).

Study participants with two or more corticosteroid injections

Of the 277 participants who had two or more corticosteroid injections, three (3/277, 1.1%) tested positive within 28 days, and eight (8/277, 2.9%) tested positive within 4 months, which was lower than the infection rate among the general population during the same period (P<.001 for the 28-day cutoff; P=.002 for up to 4 months). These participants were older than the entire cohort (63 ± 14 vs. 59 ± 15 years, P<.001). Comparisons for each phase of recovery and for all infections within 4 months from the corticosteroid injection are listed in Table 3.

Evaluation by injection site

A total of 1410 (1410/1960, 72%) participants had nonspine (joint, bursa, or tendon sheath) injections (total of 1708 injections). The remaining 550 (550/1960, 28%) participants

underwent spine injections, including epidural injections and nerve root blocks (776 injections). No difference in the COVID-19 incidence rate was seen between these groups when considering infections diagnosed both within 28 days (6/1408, 0.4% vs 4/552, 0.7%; P=.481) and up to 4 months (26/1408, 1.9% vs 17/552, 3.1%; P=.121) after the injection (Table 4).

Discussion

This prospective cohort multicenter study aimed to determine the incidence of symptomatic COVID-19 in individuals receiving fluoroscopic/US-guided corticosteroid injections for musculoskeletal pain compared with the general population during the pandemic recovery period given ongoing concern for corticosteroid-induced immunosuppression. Our main findings are: (1) participants receiving image-guided corticosteroid injections for pain management performed during the recovery period of the COVID-19 pandemic did not have associated increased rates of symptomatic COVID-19 compared with the general population (10/1960 (0.5%) vs 519,195/6,892,503 (7.5%); P<.001); (2) participants who had two or more visits for injections did not show a significantly higher infection rate than the general population (3/277 (1.1%) vs 519,195/6,892,503 (7.5%); P<.001); and (3) participants diagnosed with COVID-19 had higher BMI than the general population (32 ± 10 vs 28 ± 6 kg/m^2; P=.04).

The association between intra-articular corticosteroids and susceptibility to infection was previously questioned by Sytsma et al., who found a relative increased risk of developing influenza of 1.52 among subjects who had received corticosteroid injections (29). Other studies have shown mixed results, including a review by Youssef et al. on the risk of infection among subjects with rheumatologic diseases receiving corticosteroid treatment, with suggestion of increased risk in observational studies but not in randomized controlled trials (30).

A prior prospective study by our group showed no evidence of an increased risk of COVID-19 during the lockdown period of the current pandemic (23). Additional retrospective studies with cohorts ranging from 30 to 734 participants have shown similar results since then (19,24–26). The findings during the recovery period in our state further support the safety of intra-articular and spine corticosteroid injections during the COVID-19 pandemic. No difference in the 28-day infection rate was seen between our cohort and the general population, even when the analysis was performed separately for each phase of recovery. Most studies indicate that systemic or intra-articular corticosteroid effects on the immune system are unlikely to be significant after more than a month, but effects on the adrenal glands may persist for more than 4 weeks (4,12,13,31). Our findings were similar even when accounting for infections occurring up to 4 months after the injection.

It is interesting that the COVID-19 incidence rate in our cohort was lower than that in the general population. A few different factors could explain this finding: (1) All participants were screened for symptoms and sick contacts before their injection, which would decrease the chances of an injection being performed during the initial phases of the disease; (2) With an average age of 59 ± 15 years, we would expect most of our participants to have been employing safety measures due to a perceived higher risk of developing complications from COVID-19; (3) Since we used EMRs and phone calls to screen for laboratory test results and COVID-19 symptoms, asymptomatic infections could be missed, although a similar phenomenon would be expected among the general population.

Another feature to be considered was the duration of corticosteroid effects based on the type of medication used. Normalization of HPA suppression may take up to 1- 2 weeks for betamethasone and methylprednisolone acetate and up to four weeks for triamcinolone acetonide

(4,9,11–13,31). The main medications used for spine injections in our group are betamethasone and dexamethasone, while triamcinolone and methylprednisolone are used for joint and soft tissue injections. No differences in COVID-19 incidence rate were seen between spine (epidural injections and nerve root blocks) and nonspine (including joints, bursae, and tendon sheath) injections (P=.481), suggesting that longer-acting corticosteroids (triamcinolone and methylprednisolone) are similar to shorter-acting corticosteroids (betamethasone and dexamethasone) in terms of their risk for COVID-19.

In unadjusted analyses, participants diagnosed with COVID-19 had a higher BMI than the entire study cohort. Excess adipose tissue can affect the immune system by creating a proinflammatory state that alters the phenotype of lymphocytes, resulting in a delayed adaptive immune response (32,33). Although at least one study has shown increased odds of hospitalization for COVID-19 among patients with rheumatologic disease who were treated with systemic corticosteroids at doses ≥10 mg/day, this trend has not been seen in studies with intra-articular and spine injections, which is further supported by our findings (24–26,35).

Limitations of our study include, first, the fact that positive diagnoses of COVID-19 disease were identified based on symptoms and available test results, which could lead to asymptomatic infections being missed. Second, some participants followed by EMR data alone could have undergone COVID-19 testing in other facilities. Multivariable adjustment for risk factors was not performed.

In conclusion, patients who received fluoroscopic/US-guided image-guided corticosteroid injections for pain management performed during the recovery period had a lower incidence of symptomatic COVID-19 compared with the general population. These findings provide reassurance to providers and individuals who rely on corticosteroid injections for the

management of musculoskeletal pain during potential new COVID-19 surges, even in places with low vaccination rates.

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References

1. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. Pain Physician. 2012;15(5):371–384.
2. Chou R, Hashimoto R, Friedly J, et al. Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015;163(5):373–381. doi: 10.7326/M15-0934.
3. Lavelle W, Lavelle ED, Lavelle L. Intra-articular injections. Med Clin North Am. 2007;91(2):241–250. doi: 10.1016/j.mcna.2006.12.002.
4. Habib GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol. 2009;28(7):749–756. doi: 10.1007/s10067-009-1135-x.
5. Webster J, Sternberg E. Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. J Endocrinol. 2004;181(2):207–221. doi: 10.1677/joe.0.1810207.
6. Johnston PC, Lansang MC, Chatterjee S, Kennedy L. Intra-articular glucocorticoid injections and their effect on hypothalamic–pituitary–adrenal (HPA)-axis function. Endocrine. 2015;48(2):410–416. doi: 10.1007/s12020-014-0409-5.
7. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine Regulation of Immunity. Annu Rev Immunol. 2002;20(1):125–163. doi: 10.1146/annurev.immunol.20.082401.104914.
8. Widmer IE, Puder JJ, König C, et al. Cortisol Response in Relation to the Severity of Stress and Illness. J Clin Endocrinol Metab. 2005;90(8):4579–4586. doi: 10.1210/jc.2005-0354.
9. Dickson RR, Reid JM, Nicholson WT, Lamer TJ, Hooten WM. Corticosteroid and Cortisol Serum Levels Following Intra-articular Triamcinolone Acetonide Lumbar Facet Joint Injections. Pain Pract. 2018;18(7):864–870. doi: 10.1111/papr.12686.
10. Lazarevic MB, Skosey JL, Djordjevic-Denic G, Swedler WI, Zgradic I, Myones BL. Reduction of cortisol levels after single intra-articular and intramuscular steroid injection. Am J Med. 1995;99(4):370–373. doi: 10.1016/S0002-9343(99)80183-1.
11. Abdul AJ, Ghai B, Bansal D, Sachdeva N, Bhansali A, Dhatt SS. Hypothalamic Pituitary Adrenocortical Axis Suppression following a Single Epidural Injection of Methylprednisolone Acetate. Pain Physician. 2017;20(7):E991–E1001.
12. Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic–pituitary–adrenal axis: a randomized controlled study. Clin Rheumatol. 2014;33(1):99–103. doi: 10.1007/s10067-013-2374-4.
13. Habib G, Jabbour A, Salman J, Hakim G, Haddad H. The effect of epidural methylprednisolone acetate injection on the hypothalamic-pituitary-adrenal axis. J Clin Anesth. 2013;25(8):629–633. doi: 10.1016/j.jclinane.2013.07.002.
14. Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015;100(6):2171–2180. doi: 10.1210/jc.2015-1218.
15. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. The Lancet. 2020;395(10223):473–475. doi: 10.1016/S0140-6736(20)30317-2.
16. Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care. 2019;23(1):99. doi: 10.1186/s13054-019-2395-8.

17. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018;197(6):757–767. doi: 10.1164/rccm.201706-1172OC.
18. Morgan C, Dattani R. Should I use steroid injections to treat shoulder pain during the COVID-19 pandemic? JSES Int. 2020;4(4):709–712. doi: 10.1016/j.jseint.2020.07.023.
19. McKean D, Chung SL, Fairhead R, et al. Corticosteroid injections during the COVID-19 pandemic: experience from a UK centre. Bone Jt Open. 2020;1(9):605–611. doi: 10.1302/2633-1462.19.BJO-2020-0130.R1.
20. British Society for Rheumatology, Chartered Society of Physiotherapy, British Association of Spine Surgeons, British Orthopaedic Association. Corticosteroid use for musculoskeletal and rheumatic conditions during COVID-19 pandemic. 2020. https://www.bssh.ac.uk/_userfiles/pages/files/COVID/BOA%20Corticosteroid-use-for-musculoskeletal-and-rheumatic-conditions-during-COVID-19-Pandemic-V1.pdf.
21. Fascia D, Dalili D, Rennie W, Rowbotham E, Carne A, Robinson P. Recommendations of the British Society of Skeletal Radiologists: the safety of corticosteroid injections during the COVID-19 global pandemic. 2020. https://acpomit.csp.org.uk/system/files/documents/2021-01/musculoskeletal_radiology_during_the_covid-19_global_pandemic-rhw001180-lap.pdf.
22. American Academy of Orthopaedic Surgeons. Guidance summary: use of corticosteroids for musculoskeletal pain during the COVID-19 pandemic. . https://www.aaos.org/about/covid-19-information-for-our-members/guidance- for-elective-surgery/use-of-corticosteroids-for-musculoskeletal-pain-during-the-c ovid-19-pandemic/.
23. Chang CY, Prabhakar A, Staffa SJ, et al. Symptomatic COVID-19 infections in outpatient image-guided corticosteroid injection patients during the lockdown phase. Skeletal Radiol. 2021;50(6):1117–1123. doi: 10.1007/s00256-020-03656-w.
24. Azwan Aziz M, Abu Hanifah R, Mohd Nahar AM. Musculoskeletal Corticosteroid Injection during COVID-19 Pandemic in Sabah: Is It Safe? Schwingel PA, editor. Adv Orthop. 2021;2021:1–6. doi: 10.1155/2021/8863210.
25. Newton AC, Jones G, Jones JWM, Norris R, Barabas AG. Intra-articular corticosteroid injections during the COVID-19 lockdown period: A service evaluation. Musculoskeletal Care. 2021;19(2):236–243. doi: 10.1002/msc.1530.
26. Bugeja M, Mariani J, Dowling J, et al. Musculoskeletal steroid injections during the COVID-19 pandemic. J Orthop. 2021;26:103–106. doi: 10.1016/j.jor.2021.07.017.
27. Massachusetts Department of Public Health. COVID-19 Response Reporting. . https://www.mass.gov/info-details/covid-19-response-reporting.
28. Waljee AK, Rogers MAM, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ. 2017;357:j1415. doi: 10.1136/bmj.j1415.
29. Sytsma TT, Greenlund LK, Greenlund LS. Joint Corticosteroid Injection Associated With Increased Influenza Risk. Mayo Clin Proc Innov Qual Outcomes. 2018;2(2):194–198. doi: 10.1016/j.mayocpiqo.2018.01.005.
30. Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin N Am. 2016;42(1):157–176. doi: 10.1016/j.rdc.2015.08.004.
31. Habib G, Elias S, Abu-Elhaija M, et al. The effect of local injection of methylprednisolone acetate on the hypothalamic-pituitary-adrenal axis among patients with greater trochanteric pain syndrome. Clin Rheumatol. 2017;36(4):959–963. doi: 10.1007/s10067-016-3517-1.

32. Goossens GH, Dicker D, Farpour-Lambert NJ, et al. Obesity and COVID-19: A Perspective from the European Association for the Study of Obesity on Immunological Perturbations, Therapeutic Challenges, and Opportunities in Obesity. Obes Facts. 2020;13(4):439–452. doi: 10.1159/000510719.
33. Honce R, Schultz-Cherry S. Impact of Obesity on Influenza A Virus Pathogenesis, Immune Response, and Evolution. Front Immunol. 2019;10:1071. doi: 10.3389/fimmu.2019.01071.
34. Tartof SY, Qian L, Hong V, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. Ann Intern Med. 2020;173(10):773–781. doi: 10.7326/M20-3742.
35. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79(7):859–866. doi: 10.1136/annrheumdis-2020-217871.

Table 1. Participant Demographics

Demographic	Study cohort (n=1960)	Two or more visits (n=277)	P value	COVID-19 diagnosis within 28 days of injection (n=10)	P value	COVID-19 diagnosis within 4 months of injection (n=43)	P value
Age, years, mean ± SD (range)	59 ± 15 (19 - 97)	63 ± 14 (20 - 97)	<.001	65 ± 19 (25 - 90)	.22	59 ± 15 (21 - 90)	.93
Women	59 ± 15 (19 - 96)	63 ± 13 (27 - 96)	.01	.	.	.	.
Men	59 ± 16 (19 - 97)	63 ± 15 (20 - 97)	.01	.	.	.	.
Sex							
Women, No. (%)	1031 (53)	140 (51)	.39	5 (50)	.87	24 (56)	.67
Men, No. (%)	929 (47)	137 (49)		5 (50)		19 (44)	
BMI (kg/m2), mean ± SD (range)	28 ± 6 (15 - 61)	29 ± 6 (18 - 61)	.34	32 ± 10 (22 - 49)	.04	31 ± 7 (18 - 61)	.005
Comorbidities							
Hypertension, No. (%)	858 (44)	137 (49)	.08	4 (40)	.69	17 (39)	.44
Diabetes, No. (%)	239 (12)	41 (15)	.24	1 (10)	.78	9 (21)	.10
Immunocompromised, No. (%)	141 (7)	29 (10)	.07	2 (20)[a]	.14	3 (7)[b]	.91
Type of injection							
Spine (epidural, nerve root), No. (%)	550 (28), 776 injections	149 (49), 353 injections	-	4 (40), 6 injections	-	17 (40), 23 injections	-
Other (joint, bursa, tendon sheath), No. (%)	1410 (72), 1708 injections	128 (51), 365 injections	-	6 (60), 10 injections	-	26 (60), 34 injections	-
Total number of injections	2484	718[c]	-	16[d]	-	57[e]	-
Interval between injection and symptoms/positive test for COVID-19, days, mean ± SD (range)	-	-	-	12 ± 8 (1 – 22)	-	59 ± 33 days (1 – 118)	-

BMI: body mass index, SD: standard deviation, COVID-19: coronavirus disease 2019. [a]Chronic kidney disease, non-small-cell lung cancer on methotrexate. [b]Chronic kidney disease, non-small-cell lung cancer on methotrexate, systemic lupus erythematosus. [c]Median per participant (range): 2 (2-6). [d]One participant with 5 visits, two participants with 2 visits each. [e]One participant with 5 visits, one participant with 3 visits, and 8 participants with 2 visits each.

Table 2. Types of Corticosteroid Injections

Type of injection	Total injections (n=2484)
Spine (epidural, nerve root)	776 (31%)
Corticosteroid dose (mg)	
Mean ± SD	12 ± 3
Range	6 – 24
Laterality	
Right	366 (47%)
Left	316 (41%)
Midline (ESI)	44 (5%)
Bilateral	50 (7%)
Other (joint, bursa, tendon sheath, trigger point, peripheral nerves)	1708 (69%)
Corticosteroid dose (mg)	
Mean ± SD	40 ± 20
Range	6 – 160
Laterality	
Right	796 (47%)
Left	636 (37%)
Bilateral	276 (16%)

SD: standard deviation, ESI: epidural steroid injection.

Table 3. COVID-19 Incidence Rates

	Group 1	Group 2	Group 3	P values		
	Study Cohort	**Massachusetts Population (n=6,892,503)**	**People who had 2 or more visits for steroid injections**	**Group 1 vs Group 2**	**Group 1 vs Group 3**	**Group 2 vs Group 3**
Infections within 28 days from the corticosteroid injection						
Lockdown period (4/15/20 - 5/18/20)	1/33 (3.0%)	58,889 (0.8%)	No participants	.25	.	.
Phase I recovery (5/19/20 - 6/7/20)	0/53 (0%)	16,384 (0.2%)	0/2 (0%)	.999	.999	.999
Phase II recovery (6/8/20 - 7/12/20)	0/184 (0%)	2,193 (0.03%)	0/2 (0%)	.999	.999	.999
Phase III recovery step 1 (7/13/20 - 10/4/20)	1/660 (0.2%)	26,811 (0.4%)	0/47 (0%)	.53	.999	.999
Phase III recovery step 2 (10/5/20 - 12/13/20)	3/454 (0.6%)	147,134 (2.1%)	1/96 (1.0%)	.02	.54	.73
Rollback to Phase III recovery step 1 (12/14/20 - 2/26/21)	5/576 (0.9%)	267,784 (3.9%)	2/130 (1.5%)	<.001	.62	.25
Entire study period (4/15/20-2/26/2021)	10/1960 (0.5%)	519,195 (7.5%)	3/277 (1.1%)	<.001	.21	<.001
Infections within 4 months from the corticosteroid injection						
Entire study period (4/15/20-2/26/2021)*	43/1960 (2.2%)	519,195 (7.5%)	8/277 (2.9%)	<.001	.52	.002

* The incidence rate for each phase of recovery was not used when considering infections up to 4 months after the injection because when using the extended cutoff, some participants had their injections and diagnosis of COVID-19 occurring in different phases of recovery, which would invalidate the comparison.

Table 4. COVID-19 Incidence Rates: Spine versus Nonspine Corticosteroid Injections

COVID-19 Incidence Rate	Spine Injections	Nonspine Injections	P values
Diagnosis within 28 days	4/552 (0.7%, 95% CI 0.20-1.9%)	6/1408 (0.4%, 95%CI 0.16-0.92)	.48
Diagnosis within < 4 months	17/552 (3.1%, 95%CI 1,8-4.9%)	26/1408 (1.9%, 95%CI 1.2-2.7%)	.12

Figures

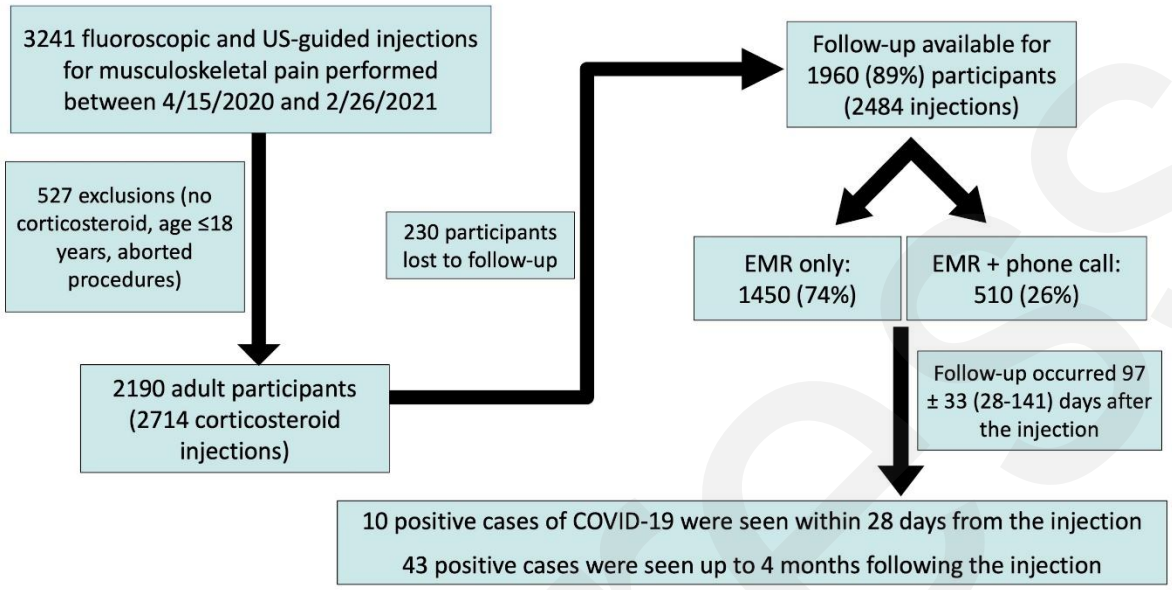


Figure 1. Flowchart depicting the image-guided corticosteroid injection participant cohort.

EMR, electronic medical record.

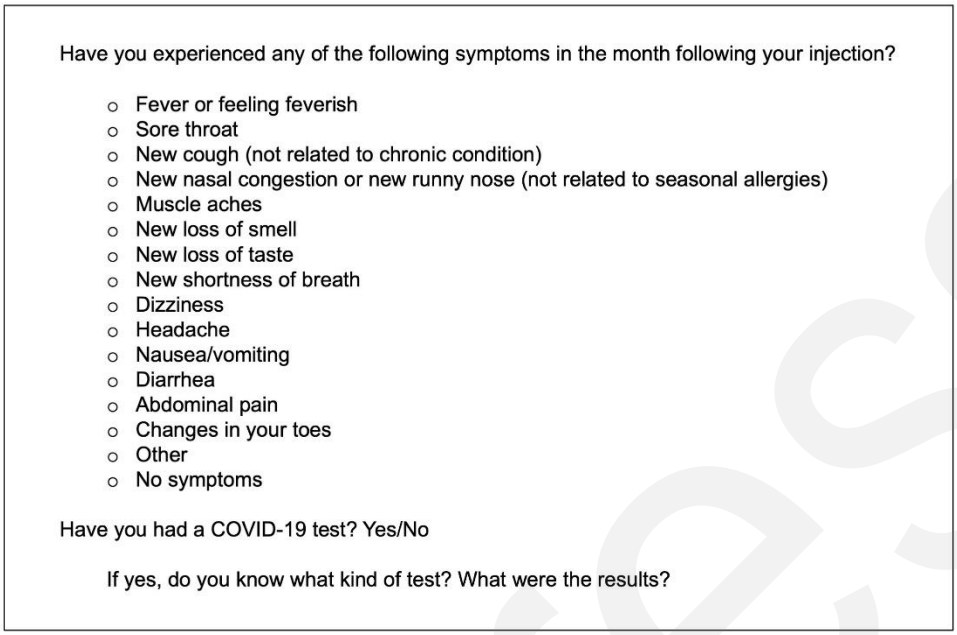
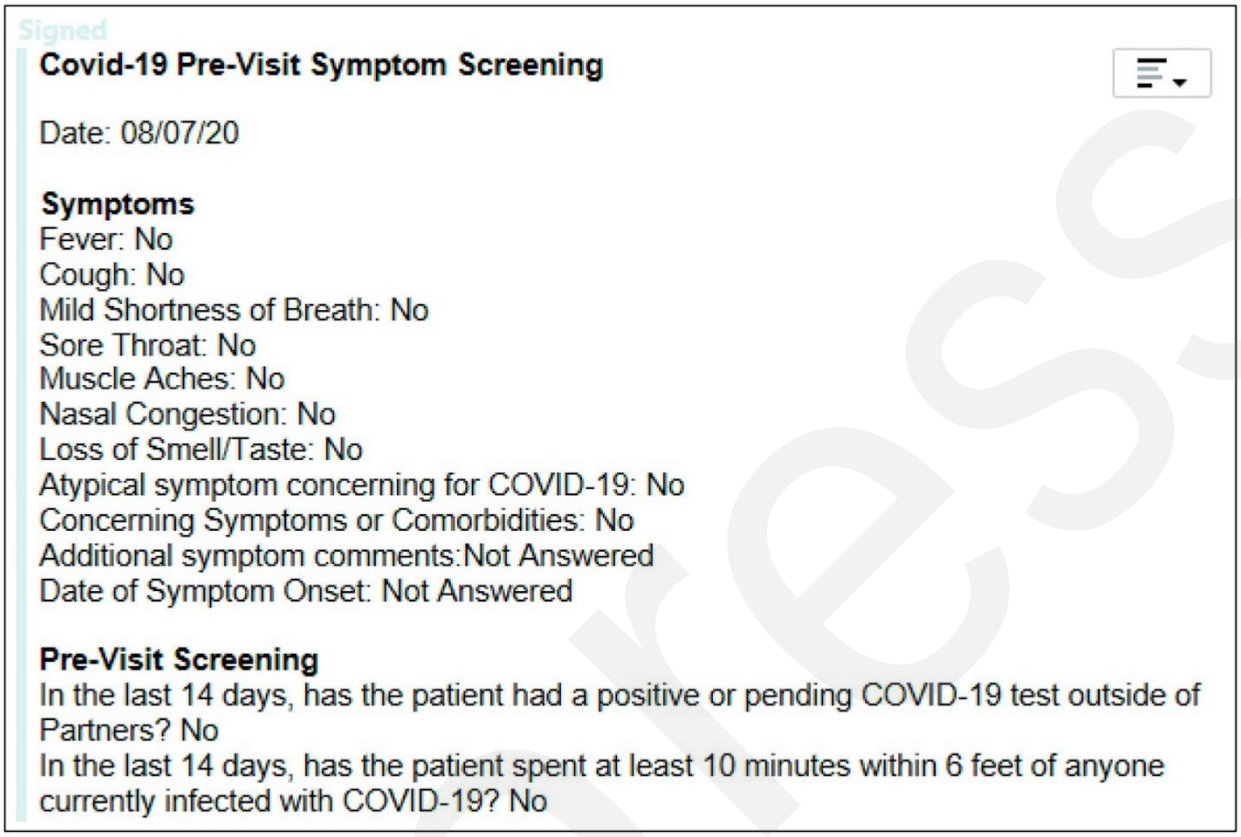


Figure 2. Postprocedure survey template for phone calls.

Appendix E1


Signed

Covid-19 Pre-Visit Symptom Screening

Date: 08/07/20

Symptoms
Fever: No
Cough: No
Mild Shortness of Breath: No
Sore Throat: No
Muscle Aches: No
Nasal Congestion: No
Loss of Smell/Taste: No
Atypical symptom concerning for COVID-19: No
Concerning Symptoms or Comorbidities: No
Additional symptom comments:Not Answered
Date of Symptom Onset: Not Answered

Pre-Visit Screening
In the last 14 days, has the patient had a positive or pending COVID-19 test outside of Partners? No
In the last 14 days, has the patient spent at least 10 minutes within 6 feet of anyone currently infected with COVID-19? No

Figure E1: COVID-19 screening questionnaire used as part of official hospital policy for in-person appointments.

Table E1. Most Common Symptoms of Participants Diagnosed with COVID-19

Symptoms	Positive cases within 28 days from the injection (n=10)	Positive cases within 4 months from the injection (n=43)
Myalgia/fatigue	6 (60%)	10 (23%)
Fever	5 (50%)	10 (23%)
Cough	4 (40%)	15 (35%)
Shortness of breath	3 (30%)	8 (19%)
Headache	2 (20%)	7 (16%)
Nasal congestion	2 (20%)	9 (21%)
Loss of smell/taste	2 (20%)	3 (7%)
GI distress (nausea, diarrhea)	1 (10%)	6 (14%)
Sore throat	1 (10%)	5 (12%)
Asymptomatic	1 (10%)	8 (19%)
Dizziness	0	1 (2%)
Not registered	0	4 (9%)