Incidence and Disease Course of COVID-19 Infection Among Unvaccinated Patients Who Received Local Corticosteroid Injections

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Objective: There are concerns that local corticosteroid injections may increase the risk of COVID-19 infection because of the immunosuppressive effect of corticosteroids. This study aimed to examine the relationship between local corticosteroid injections and the risk of COVID-19 infection.

Design: The date and type of procedure as well as the dose and type of corticosteroids used in patients who underwent local corticosteroid injections within 1 yr after the first COVID-19 case in the country were examined retrospectively and recorded. Patients who did not receive corticosteroids were included in the control group. Coronavirus disease 2019 infection histories of all patients were recorded.

Results: There was no significant difference between the patients who received local corticosteroids and the control group in terms of the incidence of COVID-19 infections, and the number of patients who needed hospitalization or intensive care treatment. In addition, it was found that the administration of two injections, the type of procedure performed, and the dose and type of steroids were not associated with the incidence or severity of COVID-19 infections.

Conclusions: It has been shown that local corticosteroid injections are not associated with the incidence of COVID-19 infections and the number of patients who need hospitalization or intensive care treatment due to COVID-19.

Key Words: COVID, Epidural, Injection, Corticosteroid

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What Is Known

- Intra-articular injection of corticosteroids increases the risk of influenza infection.

What Is New

- There was no significant difference between the patients who received epidural and intra-articular corticosteroid injections and nerve and ganglion blocks using corticosteroids and the control group in terms of the incidence of COVID-19 infections and the number of patients who needed hospitalization or intensive care treatment. In addition, it was found that the type of procedure performed and the dose and type of steroids were not associated with the incidence of COVID-19 infections or the number of patients who needed hospitalization/intensive care treatment.

Local corticosteroid injections can be used for pain palliation in various painful conditions.[1,2] The epidural region, intra-articular, peripheral nerves, or ganglia can be targeted in local corticosteroid injections, depending on the pathologic condition.[1,3]

Epidural steroid injections are used for a variety of painful conditions, particularly disc herniations. It has been shown to reduce pain and increase functionality in patients.[4–6] It has been reported in various studies that intra-articular injections, and nerve and ganglion blocks are also effective in reducing pain and improving functional status in patients.[7–10] Intra-articular steroid injections reduce pain by suppressing inflammation in conditions such as bursitis, synovitis, and arthritis. Local corticosteroid injections can sometimes delay or prevent elective surgeries in certain conditions.[11–14]

There are also systemic effects of locally injected steroids. It has been shown that the hypothalamic-pituitary-adrenocortical (HPA) axis is suppressed for up to 4–12 wks with epidural and intra-articular steroid injections.[11,15–18] Maximum HPA suppression occurs in the first 2 days. Hypothalamic-pituitary-adrenocortical suppression increases with increasing dose and frequency. Hypothalamic-pituitary-adrenocortical suppression times vary according to the type of steroid administered and the liver and kidney functions of the patient.[16,19]

Corticosteroids have been reported to have an immunosuppressive effect. It suppresses the immune system in a dose-dependent manner.[20] Steroids are known to negatively affect the adaptive and innate immune systems.[21] Corticosteroids produce this immunosuppressive effect by inhibiting phagocytes, suppressing inflammatory genes, and upregulating anti-inflammatory genes.[22] It has also been reported that corticosteroids contribute to the immunosuppressive effect by increasing glucose levels. Corticosteroids suppress mediators such as macrophage migration inhibition factor and interleukins and induce anti-inflammatory mediators.[23] It is also known that steroids reduce

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The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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the production of immunoglobulin A and immunoglobulin G from plasma cells.[24] Intra-articular corticosteroid use has been shown to increase the incidence of influenza.[25]

Concerns have therefore arisen that corticosteroids may increase the risk of COVID-19 infection.[26] Several guidelines have been published on COVID-19 and local injections of corticosteroids in the period before to the initiation of COVID-19 vaccination. For example, a clinical perspective has been published on behalf of the Spine Intervention Society, which states that corticosteroid therapy should not be administered during the pandemic. They reported that there was a need for studies examining the relationship between corticosteroid injections and the risk of COVID-19 infection.[21]

The British Orthopedic Association, the British Society of Rheumatology, the British Association of Spinal Surgeons, and the Association of Chartered Physiotherapists in Orthopedic Medicine and Injection Therapy recommended that low doses should be used and that corticosteroid injections should be given only in cases of acute synovitis. They suggested that if they were to be performed for noninflammatory musculoskeletal pain, they should be given only if the patient did not respond to other treatments and had debilitating pain.[19]

The British Society of Skeletal Radiologists recommended that corticosteroid injections should be avoided as much as possible during the COVID-19 pandemic and should not be given to those with comorbidities and the older people.[19]

There are limited data on whether local corticosteroids increase the risk of COVID-19 infections.[11,19,27] This study aimed to investigate the relationship between local steroid injections administered via intra-articular and epidural injections and nerve/ganglion blocks and the incidence of COVID-19 infections and the number of patients requiring hospitalization and intensive care treatment due to COVID-19.

METHODS

This retrospective study was approved by the Marmara University Faculty of Medicine Ethics Committee (no: 09.2022.105, date: July 1, 2022). This study conforms to all Strengthening the Reporting of Observational Studies in Epidemiology guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B886).

Among the patients who presented to the Marmara University Medical Faculty Hospital Pain outpatient clinic during the 1 yr between March 11, 2020, when the first case of COVID-19 was seen in Turkey, and March 11, 2021, those who underwent epidural and intra-articular steroid injections, and patients who underwent nerve and ganglion blockade using steroids were included in the study. Verbal consent was obtained from the participants with the approval of the ethics committee. The inclusion criteria were as follows: being older than 18 yrs and having undergone epidural injections, intra-articular injections, and nerve or ganglion block using corticosteroids between March 11, 2020, and March 11, 2021.

The exclusion criteria were the use of immunosuppressant medication, having received a COVID vaccine, the presence of any disease that suppressed the immune system (e.g., HIV infection, systemic lupus erythematosus, systemic inflammatory diseases), and disease associated with primary immunodeficiency (e.g., CTLA4 deficiency, autoimmune lymphoproliferative syndrome). At the time of the study, vaccination was not yet widespread in the country where the study was conducted. Three patients in the control group had received only a single dose of the COVID-19 vaccine and had not yet received their second dose. In the injection group, none of the patients had yet been vaccinated. Three patients in the control group who had a single dose of vaccine were excluded from the study because none of the patients in the injection group were vaccinated. Thus, all patients included in the study consisted of patients who did not receive the COVID-19 vaccine.

Patients who visited the same outpatient clinic between the same dates for knee pain but did not receive corticosteroids at least 1 yr before or after the procedure were included in the control group. The exclusion criteria of the corticosteroid group were also applied to the control group.

The patients were asked about their height, weight, and the medications they used over the phone.

The ages; sexes; drugs used; COVID-19 histories; hospitalization and intensive care histories; and types, dates, and doses of COVID-19 vaccine of the patients in both groups were recorded through the hospital information system and the national patient information system (e-Nabız), which allows seeing laboratory test results, diagnoses, and treatments in all health institutions and hospitals in the country.

Comorbidities (immunocompromised state, heart disease, diabetes mellitus, and chronic lung disease) determined for the population at risk for COVID-19 by the Centers for Disease Control and Prevention were questioned and recorded.[21] A positive COVID-19 polymerase chain reaction test or a diagnosis of COVID-19 in any health center was considered significant in terms of COVID-19 positivity. In addition, the date and type of the procedures performed as well as the dose and type of corticosteroid used were recorded for the patients who received corticosteroid injections. The outpatient visit dates of the control group were recorded.

STATISTICAL ANALYSES

Statistical analyses of the study were performed using the Statistical Package for the Social Sciences version 25.0 software for Windows (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp, Armonk, NY). Power analysis was performed using the G*Power 3.1.9.6 software package (Franz Foul, Universitat Kiel, Germany).

Normality assumption for quantitative variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For the univariate analysis of the variables in the study, the Kruskal-Wallis test, Mann-Whitney U test, χ^2 test, and Fisher-Freeman-Halton exact tests were used according to the type of variable and the availability of assumptions. The descriptive statistics of the variables are given as mean ± SD, median (min–max), and frequencies (number and percentage, n [%]). In all statistical analyses, cases with a P value less than 0.05 were interpreted as statistically significant.

The sample size of the study was calculated by performing priori power analysis before the study. For the χ^2 test, effect size $w = 0.15$, power $(1 - \beta) = 0.80$, $df = 2$ was taken, and as a result of the power analysis, it was calculated that the total sample size should be at least 486. According to the results of the post hoc analysis, a computed achieved power test was

performed to determine the power of the study at the end of the study; the power values of all tests used were greater than 0.90.

RESULTS

Three hundred seventy-nine patients who received corticosteroid injections and 434 patients from the control group were evaluated for inclusion in the study. Twenty patients from the corticosteroid-treated patients and 19 patients from the control group were excluded because they had at least one exclusion criterion. Ninety-one patients who received corticosteroid injections and 104 patients in the control group were excluded from the study because they did not have a registered telephone number for contact. Three patients in the control group who had a single dose of vaccine were excluded from the study because none of the patients in the injection group were vaccinated. As a result, 308 patients in the control group and 268 patients who underwent corticosteroid injections were included in the study (Fig. 1). Of the patients who received corticosteroid injections, 15 patients who received double injections were allocated to group B, and 253 patients who received single corticosteroid injections comprised group A. The difference between the groups in terms of age, sex, body mass index, comorbidities, and the number of patients who had COVID-19 infections before the procedure was not statistically significant ($P > 0.05$). There was no significant relationship between the groups in terms of the number of patients who had COVID-19 infections within 3 or 6 mos or at any time after the procedure or outpatient clinic visit. Likewise, there was no statistically significant difference between the groups in terms of the number of patients hospitalized or in need of intensive care unit treatment due to COVID-19 ($P > 0.05$; Table 1). The injection sites of local corticosteroids administered to patients are listed in Table 2.

There was no significant difference between the groups divided according to steroid doses in terms of the number of patients who had COVID-19 infections within 3 or 6 mos after the procedure/outpatient clinic visit or at any time and also the number of patients hospitalized because of COVID-19 or in need of intensive care treatment ($P > 0.05$; Table 3).

When the patients were grouped and compared according to the type of procedure performed, no significant difference was found between the groups (Table 4).

DISCUSSION

In this study, there was no significant difference in the number of patients infected with COVID-19, hospitalized because of COVID-19, or in need of intensive care treatment in patients who received epidural and intra-articular corticosteroid injections or who underwent nerve and ganglion blocks using corticosteroids compared with those who did not receive corticosteroids. It was also found that the type of procedure performed or the amount of steroid dose used was not statistically significant in terms of the incidence of COVID-19 infection.

Musculoskeletal symptoms constitute an important part of visits to health centers.[28] In these patients, when there is no response to conservative treatment, local corticosteroid injections can be performed to control the symptoms.[1,2] However, because of the immunosuppressive effects of corticosteroids, various concerns have arisen regarding the risk of COVID-19

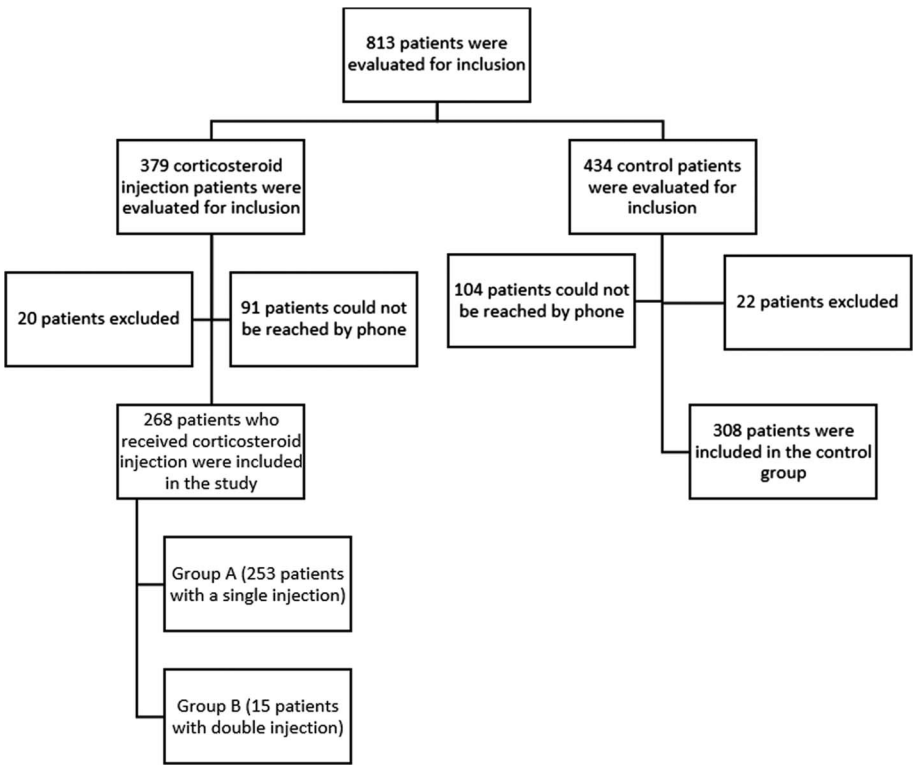

FIGURE 1. Flow of participants in this study.

TABLE 1. Comparison of clinical and demographic characteristics of patients

	Control Group (n = 308)	Group A (n = 253)	Group B (n = 15)	P
Age, mean ± SD	58.09 ± 13.35	58.12 ± 13.88	54.73 ± 10.15	0.631[a]
Median (min–max)	58.0 (20.0–92.0)	59.0 (18.0–92.0)	55.0 (35.0–72.0)	
Sex				
Male	112 (36.4%)	84 (33.2%)	5 (33.3%)	0.731[b]
Female	196 (63.6%)	169 (66.8%)	10 (66.7%)	
BMI, mean ± SD	27.70 ± 4.81	28.65 ± 5.40	28.24 ± 4.42	0.066[a]
Median (min–max)	27.0 (18.4–56.6)	27.7 (18.4–63.1)	27.8 (21.1–37.5)	
No. patients with chronic lung disease	46 (15.6%)	36 (14.2%)	2 (13.3%)	0.891
No. patients with diabetes mellitus	66 (21.4%)	57 (22.5%)	3 (20.0%)	0.937
No. patients with chronic heart disease	42 (13.6%)	29 (11.5%)	2 (13.3%)	0.741
No. patients with COVID-19 before injection/outpatient visit	20 (6.49%)	8 (3.16%)	0 (0.0%)	0.151[c]
No. patients with COVID-19 after injection/outpatient visit	64 (20.78%)	57 (22.53%)	4 (26.67%)	0.740
No. patients with COVID-19 within 3 mos of injection/outpatient visit	8 (2.60%)	8 (3.16%)	0 (0.0%)	0.864
No. patients with COVID-19 within 6 mos of injection/outpatient visit	28 (9.09%)	20 (7.91%)	0 (0.0%)	0.583
No. patients hospitalized for COVID-19 after injection or outpatient visit	10 (15.63%)	14 (24.56%)	1 (25.00%)	0.393
No. patients in need of intensive care treatment unit due to COVID-19 after injection or outpatient clinic visit	1 (0.32%)	1 (0.40%)	0 (0.0%)	0.999

[a] Kruskal-Wallis test.
[b] χ^2 test.
[c] Fisher-Freeman-Halton exact test.
BMI, body mass index; max, maximum; min, minimum.

in corticosteroid injections.[26] Many guidelines have been published advocating avoiding corticosteroid injections throughout the pandemic. However, the organizations that published these guidelines have declared that this cautious approach in the guidelines is based on the known general immunosuppressive effects of corticosteroids and studies showing that local corticosteroid injections increase some viral infectious diseases, such as influenza. They reported that studies were needed to show the relationship between local corticosteroid injection and the risk of COVID-19 infections.[19,21]

TABLE 2. Injection sites of local corticosteroids administered to patients

	No. Patients	%
Lumbar epidural	111	41.4
Caudal epidural	44	16.4
Cervical epidural	26	9.7
Knee intra-articular	22	8.2
Shoulder intra-articular	11	4.1
Hip intra-articular	10	3.7
Genicular nerve block	7	2.6
Trigeminal nerve block	6	2.2
Stellate ganglion block	5	1.9
Greater occipital nerve block	4	1.5
Intercostal nerve block	4	1.5
Superior hypogastric plexus block	3	1.1
Celiac plexus block	3	1.1
Suprascapular nerve block	3	1.1
Thoracic epidural	2	0.7
Impar block	2	0.7
Sacroiliac intra-articular	1	0.4
Pudendal nerve block	1	0.4
Lumbar sympathetic block	1	0.4
Ilioinguinal nerve block	1	0.4
Facet medial branch block	1	0.4
Total	268	100.0

McKean et al.,[27] in their retrospective observational study, found that the incidence of COVID-19 was quite low in 443 patients who received corticosteroid injections between February 1, 2020, and June 30, 2020. Reverse transcriptase polymerase chain reaction was performed in nine of these patients (2% of those with CSI), and all of their tests were negative. Five patients (1.1%) tested positive for SARS-CoV-2 immunoglobulin G antibodies, but all were asymptomatic.[27] In a retrospective study, Azwan Aziz et al.[11] found that none of the 35 patients who underwent corticosteroid injection between December 1, 2019, and June 30, 2020, in orthopedics and sports medicine clinics, were found to have COVID-19. Chang et al.[29] followed 71 patients who were injected with corticosteroids for 45 ± 22 days (19–83 days). They found that only one patient (1.52%) developed COVID-19. Other than the study by Chang et al.,[29] we could not find any study in the literature that included epidural procedures.

When Bugeja et al.[19] checked the status of patients who received corticosteroid injections during the COVID-19 pandemic after 30 days, they found that the incidence of COVID-19 infections was similar to the control group. We could not find any other study in the literature that included a control group, other than the study of Bugeja et al.[19] In the current study, a control group was also formed to better reveal the relationship between corticosteroid injections and the risk of

TABLE 3. Comparison of COVID-19 states according to corticosteroid doses used

	12-mg Dexamethasone (n = 17)	40-mg Triamcinolone (n = 65)	80-mg Triamcinolone (n = 171)	P^a
No. patients infected with COVID-19 after injection	3 (17.65%)	12 (18.46%)	42 (24.56%)	0.595
No. patients infected with COVID-19 within 3 mos after injection	0 (0.0%)	2 (3.08%)	6 (3.51%)	0.999
No. patients infected with COVID-19 within 6 mos after injection	0 (0.0%)	3 (4.62%)	17 (9.94%)	0.248
No. patients hospitalized for COVID-19 after injection	1 (5.88%)	3 (4.62%)	12 (7.02%)	0.299
No. patients in need of intensive care treatment due to postinjection COVID-19	0 (0.0%)	1 (1.54%)	0 (0.0%)	0.322

[a] Fisher-Freeman-Halton exact test.

COVID-19 infections. Considering the possibility of contamination from the hospital they visited for the procedure, other patients who visited the hospital were included in the control group. Among the patients who visited the outpatient clinic, the most suitable patient group in terms of number was patients with knee pain. While there were patients with different diagnoses such as low back pain and neck pain in the intervention group, the presence of only patients with knee pain in the control group was an important limitation of this study. Although there is no evidence that the difference in the body region where the patient complains of pain affects the risk of COVID-19, the fact that the groups are not fully matched is a potential confounder. In addition, because of the retrospective nature of the study, it could not be determined why some patients received cortisone injections and some did not.

Corticosteroids suppress the immune system in a dose-dependent manner. It is known that HPA suppression increases as the dose increases.[16,19] In a study, the rate of patients with HPA suppression 1 wk after 80-mg methylprednisolone injections was found to be higher (86%) than in those who received 40 mg (53%).[30] The World Institute of Pain Benelux Working Group reported that epidurally administered steroid doses should be used at the lowest possible dose.[22] Therefore, the doses administered in the present study were compared. However, there was no difference between the doses in terms of the incidence of COVID-19 infections. Likewise, it has been shown that the area where corticosteroids are administered (epidural, intra-articular, nerve, or ganglion) is not associated with the incidence of COVID-19 infection. The frequency of steroid administration is also known to increase HPA suppression.[16,19] Therefore, in the current study, those who received double injections and those who received a single injection were compared, and no significant difference was found between the two groups in terms of the incidence of COVID-19 infections.

Longer-acting steroids (methylprednisolone and triamcinolone) have been shown to suppress cortisol production for longer than steroids with fewer particles (betamethasone and dexamethasone).[31] Therefore, in the present study, dexamethasone and triamcinolone were also compared. However, it was found that the type of steroid used was not significantly associated with the incidence of COVID-19 infections.

Although it was shown that steroids took up to 12 wks to suppress the HPA, the incidence of COVID-19 infections in the 6 mos and later period of the patients was also examined because it was not known how long the immunosuppressive effect lasted. However, no significant difference was found between the groups in terms of the incidence of COVID-19 infections in any period.

The retrospective nature of the study is one of the most important limitations. In addition, because of the nature of COVID-19 infections, some patients may be asymptomatic or mild. This study could not include patients who were asymptomatic or who did not present to the hospital because of their

TABLE 4. Comparison of COVID-19 states according to the type of procedure

	Epidural Injection (n = 174)	Ganglion/Peripheral Nerve Block (n = 41)	Intra-articular Injection (n = 38)	P^a
No. patients infected with COVID-19 after injection	44 (25.29%)	5 (12.20%)	8 (21.05%)	0.191[a]
No. patients infected with COVID-19 within 3 mos after injection	13 (7.47%)	1 (2.44%)	1 (2.63%)	0.453[b]
No. patients infected with COVID-19 within 6 mos after injection	16 (9.20%)	2 (4.88%)	2 (5.26%)	0.674[b]
No. patients hospitalized for COVID-19 after injection	14 (8.05%)	0 (0.00%)	2 (5.26%)	0.126[b]
No. patients in need of intensive care treatment due to postinjection COVID-19	0 (0.00%)	1 (2.44%)	0 (0.00%)	0.311[b]

[a] χ^2 test.

[b] Fisher-Freeman-Halton exact test.

mild course and therefore were not diagnosed. However, this was true for both groups. In addition, at the time of the current study, vaccination had not yet started widely in the country where the study was conducted. Therefore, the participants in the current study were unvaccinated at the time of injections or outpatient visits. Therefore, there is a need for studies on the effect of corticosteroid injections on the incidence of COVID-19 in vaccinated individuals. In the intervention group, there were participants with different diagnoses, such as low back pain and neck pain. The fact that the control group consisted of only patients with knee pain caused the groups to be poorly matched. Although there is no evidence that the difference in the aching body region changes the risk of COVID-19, the fact that the control group consisted of only patients with knee pain was one of the most important limitations of this study. In addition, in this retrospective study, it was not recorded why the injection was not applied to the patients, and it was not evaluated at the end of the study. This is one of the limitations of the study. Despite all these limitations, this study's evaluation of the effect of local corticosteroids on the incidence of COVID-19 infections with a control group and a relatively large number of participants and being one of the few studies in this area are strengths of this study.

In conclusion, it was determined that local corticosteroid injections (epidural, intra-articular injections, and nerve/ganglion blocks) were not associated with an increased incidence of COVID-19 infections and the need for hospitalization/intensive care unit treatment. It was also found that the type of procedure performed, and the dose and type of corticosteroid used were not associated with an increased incidence of COVID-19 infections and the need for hospitalization/intensive care unit treatment. Further studies are needed in this regard.

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