The Effect of the Timing of Dexamethasone Administration in Patients with COVID-19 Pneumonia

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Research

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Abstract

Introduction: Despite the proven benefits of dexamethasone in hospitalized COVID-19 patients, the optimum time for the administration of dexamethasone is unknown. We investigated the progression of COVID-19 pneumonia based on the timing of dexamethasone administration.

Methods: A single-center, retrospective cohort study based on medical record reviews was conducted between June 10 and September 21, 2020. We compared the risk of severe COVID-19, defined as the use of a high-flow nasal cannula or a mechanical ventilator, between groups that received dexamethasone either within 24 hours of hypoxemia (early dexamethasone group) or 24 hours after hypoxemia (late dexamethasone group). Hypoxemia was defined as room-air SpO_2 <90%.

Results: Among 59 patients treated with dexamethasone for COVID-19 pneumonia, 30 were in the early dexamethasone group and 29 were in the late dexamethasone group. There was no significant difference in baseline characteristics, the time interval from symptom onset to diagnosis or hospitalization, or the use of antiviral or antibacterial agents between the two groups. The early dexamethasone group showed a significantly lower rate of severe COVID-19 compared to the control group (75.9% vs 40.0%, P-value=0.012). Further, the early dexamethasone group showed a significantly shorter total duration of oxygen supplementation (10.45 d *vs.* 21.61 d, P-value=0.003) and length of stay in the hospital (19.76 d *vs.* 27.21 d, P-value=0.013). However, extracorporeal membrane oxygenation and in-hospital mortality rates were not significantly different between the two groups.

Conclusions: Early administration of dexamethasone may prevent the progression of COVID-19 to a severe disease, without increased mortality.

Introduction

Systemic administration of corticosteroids has been associated with decreased in-hospital mortality in coronavirus disease 2019 (COVID-19) patients with hypoxemia [1]. Among systemic corticosteroids, dexamethasone has been demonstrated to improve mortality in COVID-19 patients in two randomized controlled trials (RCTs) [2, 3], but the benefit of hydrocortisone or methylprednisolone is not as clear [1, 4, 5]. However, 36.2% (166/459) of patients who used dexamethasone eventually died [1], suggesting that dexamethasone should be used in selective patients [6]. There is little information concerning the prognosis for COVID-19 patients that relates to different times of dexamethasone administration.

The efficacy of dexamethasone in protecting against acute respiratory distress syndrome (ARDS) is likely to be related to the time of initial drug administration. A recent RCT showed that dexamethasone administration within 30 hours of ARDS onset decreased the duration of mechanical ventilation and mortality rates [7]. COVID-19 studies also showed a potential benefit of early dexamethasone treatment in improving the prognosis in patients with acute respiratory failure. In the CoDEX trial, dexamethasone administration within 48 hours of the onset of ARDS significantly increased ventilator-free days in the COVID-19 patients [3]. A quasi-experimental study of moderate-to-severe COVID-19 cases found that systemic corticosteroid administered from the first day of oxygen supplementation reduced a composite of primary outcomes, including intensive care unit (ICU) care, progression to respiratory failure, and in-hospital mortality [8]. In addition, there was a positive correlation between early corticosteroid treatment and a better clinical prognosis in severe acute respiratory syndrome [9].

The timing of dexamethasone administration is of special concern in those COVID-19 patients who need oxygen therapy. This study determined whether there is a difference in the rate of ARDS progression, based on the time of dexamethasone administration, in COVID-19 patients who needed supplemental oxygen, but did not require oxygen delivery through high-flow nasal cannula or a mechanical ventilator.

Material And Methods

Study design and participants

Our study design was in accordance with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [10]. The present retrospective cohort study included all the hospitalized patients who received dexamethasone for COVID-19 pneumonia at Boramae Medical Center, Seoul, between June 10 and September 21, 2020. A diagnosis of COVID-19 was

confirmed through quantitative reverse transcription-polymerase chain reaction (RT-qPCR) assays using upper or lower respiratory tract samples.

Patients were admitted to the isolation ward for COVID-19 management, which has negative pressure ventilation. Dexamethasone was administrated to the COVID-19 patients who required oxygen therapy or had a significant desaturation (a change in pulse oximeter oxygen saturation [SpO_2] > 4%) with clinical signs of aggravated pneumonia. The time of dexamethasone administration was determined by the attending physician. Oxygen supplementation was initiated when patients had a room-air SpO_2 < 90%, which is defined as hypoxemia. Oxygen saturation was monitored through pulse oximetry for 24 hours during oxygen supplementation. Administration of remdesivir was allowed in the patients who met all of the following criteria: 1) pneumonic infiltration was evident in a chest X-ray or chest computed tomography scan, 2) room-air SpO_2 < 94%, 3) oxygen supplementation, and 4) ≤ 10 days since symptom onset. In practice, remdesivir was administered only to patients over 70 years of age because of the limited supply of remdesivir during the study period. Administration of antibiotics for respiratory infections was also allowed when a bacterial infection had not been ruled out.

Eligibility criteria

The eligibility criteria were: 1) age > 18 years old, 2) detection of SARS-CoV-2 by an RT-qPCR assay of upper or lower respiratory sample, 3) evidence of pneumonia in a chest X-ray or chest computed tomography scan (CT), and 4) administration of dexamethasone before initiation of high-flow nasal cannula (HFNC) treatment or a mechanical ventilator (MV). Exclusion criteria were immunosuppressive diseases, treatment with a systemic corticosteroid or other immunosuppressive drugs, pregnancy, terminal-stage cancer, or other end-stage diseases.

Variables and measurements

Demographic information for the study population was collected, including age, sex, body mass index, smoking status, Charlson comorbidity index (CCI), and underlying diseases (hypertension, diabetes, cerebrovascular disease, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, and cancer). Symptoms of COVID-19 were determined by medical staff when dexamethasone treatment was initiated, including abnormal senses of smell or taste, myalgia, sore throat, cough, sputum, chest discomfort, dyspnea, fever or chills, rhinorrhea, and nausea or diarrhea. Clinical severity was evaluated using the sequential organ failure assessment (SOFA) score and the simplified acute physiology score (SAPS) II using vital sign records and laboratory test results at the time of hospital admission. Laboratory tests including assays for white blood cells, lymphocytes, procalcitonin, lactate dehydrogenase, and troponin-I. Treatment information included the use of antiviral or antibacterial agents, total dose of dexamethasone, duration of dexamethasone treatment, and the time interval from symptom onset or diagnosis to initiation of dexamethasone administration.

Study outcomes

The primary outcome was to compare the rate of HFNC or MV treatments between the group receiving dexamethasone within, or before, 24 hours of hypoxemia (early dexamethasone group) and the group receiving dexamethasone 24 hours or more after hypoxemia (late dexamethasone group). The secondary outcome was to compare the total duration of oxygen supplementation and the length of stay in hospital for the two groups.

Statistical analyses

Demographic information, symptoms, clinical features, clinical severity, and study outcomes were compared between the early and late dexamethasone groups. Categorical variables were analyzed with Pearson's chi-squared test or the Fisher's exact test. Continuous variables were analyzed with the Student's t-test or Mann–Whitney U test. Logistic regression analysis was used to determine whether the timing of dexamethasone administration correlated with HFNC or MV treatments by calculating odds ratios (ORs) and 95% confidence intervals (CIs). To exclude potential bias due to confounding factors associated with the use of HFNC or MV treatments, we conducted a multivariate analysis. Independent variables were selected on the basis of their statistical significance in the univariate analysis. The criterion for inclusion of a variable in the multivariate analysis was based on the clinical significance. The Kaplan–Meier curve was used to visualize the difference in the time to HFNC or MV treatment between the early and late dexamethasone groups, and the statistical significance was estimated by the log-rank test. Univariable and multivariable Cox regression analyses were used to evaluate hazard ratios (HRs) for prolonged time to HFNC or MV treatments. Multivariable analyses were conducted using three models. Model 1 was adjusted by baseline characteristics including current smoking status and CCI. Model 2 was adjusted by clinical severity including SOFA score and SAPS II. Model 3 was adjusted by treatment-related factors including lymphocyte count and remdesivir

treatment. We considered P-values < 0.05 as statistically significant. All the statistical analyses were conducted using R statistical software (R Core Team, version 3.5.1, 2018, Vienna, Austria).

Ethics

The Institutional Review Board Committee of Seoul National University Hospital approved the study protocol and waived the need for informed consent for access to the electronic medical records (IRB No. 20-2020-33).

Results

Among a total of 212 patients hospitalized for treatment of COVID-19, 62 (29.2%) were treated with dexamethasone. After excluding three patients who received dexamethasone after HFNC treatment, 59 (27.8%) patients were placed in two groups: an early dexamethasone group (30 patients) and a late dexamethasone group (29 patients) (Fig. 1). The time interval from symptom onset to diagnosis of COVID-19 was a median 3.0 (interquartile range [IQR] = 0–5.0) days. The median time interval from symptom onset to hospitalization for COVID-19 was 3.0 (IQR = 1.0–6.5) days. All the patients showed evidence of pneumonic infiltration in the initial chest X-ray at admission.

Baseline characteristics and clinical features of the study population

In baseline characteristics, age, percentage of current smokers, and CCI were higher in the late dexamethasone group, but the values were not statistically significant (Table 1). The frequency of each symptom was not significantly different between the early and late dexamethasone groups.

Table 1
Baseline characteristics, clinical features, and clinical outcomes of COVID-19 patients in early and late dexamethasone groups

	Late dexamethasone group (n = 29)	Early dexamethasone group (n = 30)	P-value
Age, mean (± SD)	70.07 (13.87)	65.53 (14.39)	0.138
Female (%)	12 (41.4)	10 (33.3)	0.712
Body mass index, mean (± SD)	24.32 (4.64)	24.68 (4.33)	0.764
Current smoker (%)	5 (17.2)	2 (6.7)	0.394
Charlson comorbidity index, mean (± SD)	4.34 (2.06)	3.50 (2.35)	0.147
Underlying disease			
Hypertension (%)	15 (51.7)	15 (50.0)	1.000
Diabetes mellitus (%)	10 (34.5)	9 (30.0)	0.928
Cerebrovascular disease (%)	4 (13.8)	5 (16.7)	1.000
Cardiovascular disease (%)	7 (24.1)	4 (13.3)	0.465
Chronic lung disease (%)	5 (17.2)	3 (10.0)	0.666
Chronic kidney disease (%)	2 (6.9)	5 (16.7)	0.449
Chronic liver disease (%)	3 (10.3)	3 (10.0)	1.000
Cancer (%)	5 (17.2)	2 (6.7)	0.394
Symptoms			
Abnormality in sense of smell and taste (%)	2 (6.9)	2 (6.7)	1.000
Myalgia (%)	12 (41.4)	10 (33.3)	0.712
Sore throat (%)	3 (10.3)	6 (20.0)	0.503
Cough (%)	16 (55.2)	13 (43.3)	0.516
Sputum (%)	12 (41.4)	8 (26.7)	0.358
Chest discomfort (%)	1 (3.4)	3 (10.0)	0.629
Dyspnea (%)	18 (62.1)	15 (50.0)	0.502
Febrile or chilling sense (%)	14 (48.3)	20 (66.7)	0.244
Rhinorrhea or nasal obstruction (%)	0 (0.0)	1 (3.3)	1.000
Gastrointestinal symptoms (%)	4 (13.8)	3 (10.0)	0.962
No symptoms (%)	3 (10.3)	2 (6.7)	0.968
Clinical features			
Clinical severity			
SOFA score at admission	2.97 (1.32)	3.17 (1.72)	0.618

[a] oxygen supplementation includes oxygen inhalation through nasal prong, facial mask, high flow nasal cannula, mechanical ventilator, and extracorporeal membrane oxygenation.

[b] data regarding total duration of oxygen supplementation and length of stay in hospital were missing for 1 patient in early dexamethasone group and 1 patient in late dexamethasone group.

The continuous variables are expressed as the mean (± standard deviation) or the median (interquartile range) and the categorical variables are expressed as the number of patients (percentage).

IQR, interquartile range; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment

	Late dexamethasone group (n = 29)	Early dexamethasone group (n = 30)	P-value
SAPS II at admission	22.59 (5.93)	19.97 (5.24)	0.077
Laboratory test			
White blood cell counts, mean (± SD)	6534.14 (2670.09)	5795.67 (3497.94)	0.367
The number of lymphocytes, mean (± SD)	1018.14 (519.63)	1038.80 (381.86)	0.862
Procalcitonin ng/ml, median (IQR)	0.05 (0.04–0.09)	0.08 (0.05–0.16)	0.181
Lactate dehydrogenase IU/L, mean (± SD)	400.18 (130.73)	325.45 (148.33)	0.049
Troponin-I ng/ml, median (IQR)	9.35 (4.23–14.10)	10.00 (5.10–18.30)	0.783
Treatment			
Remdesivir (%)	13 (44.8)	12 (40.0)	0.911
Antibiotics (%)	29 (100.0)	30 (100.0)	NA
Total accumulative dose of dexamethasone mg, mean (± SD)	62.62 (33.34)	64.17 (32.48)	0.857
Total duration of dexamethasone mg, mean (± SD)	10.66 (5.58)	10.57 (4.48)	0.947
Time interval from symptom onset to dexamethasone administration d, mean (± SD)	7.76 (3.59)	7.03 (3.50)	0.435
Time interval from diagnosis to dexamethasone administration d, mean (± SD)	4.14 (3.26)	4.70 (3.67)	0.537
Clinical outcomes			
High flow nasal cannula or mechanical ventilation (%)	22 (75.9)	12 (40.0)	0.012
Extracorporeal membrane oxygenation (%)	2 (6.9)	0 (0.0)	0.457
Total duration of oxygen supplementation [a, b] d, mean (± SD)	21.61 (16.42)	10.45 (9.39)	0.003
Length of stay in hospital [b] d, mean (± SD)	27.21 (13.28)	19.76 (8.05)	0.013
In-hospital death (%)	1 (3.4)	1 (3.3)	1.000

[a] oxygen supplementation includes oxygen inhalation through nasal prong, facial mask, high flow nasal cannula, mechanical ventilator, and extracorporeal membrane oxygenation.

[b] data regarding total duration of oxygen supplementation and length of stay in hospital were missing for 1 patient in early dexamethasone group and 1 patient in late dexamethasone group.

The continuous variables are expressed as the mean (± standard deviation) or the median (interquartile range) and the categorical variables are expressed as the number of patients (percentage).

IQR, interquartile range; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment

In terms of clinical features, there were no significant differences in the SOFA scores or the SAPS II at admission between the two groups (Table 2). Serum lactate dehydrogenase levels were higher in the late dexamethasone group. In terms of treatments, the rate of remdesivir use or antibiotic use was very similar in the early and late dexamethasone groups. The dose of dexamethasone and the duration of dexamethasone treatment were similar between the two groups. Two patients in the early dexamethasone group started dexamethasone 1.5 (± 0.7) days before oxygen supplementation because they showed imminent hypoxemic respiratory failure with fever, a progression of pneumonic infiltration, and decreasing SpO_2.

Table 2
Clinical features and outcomes of COVID-19 patients in early and late dexamethasone groups

	Late dexamethasone group (n = 29)	Early dexamethasone group (n = 30)	P-value
Clinical features			
Clinical severity			
SOFA score at admission	2.97 (1.32)	3.17 (1.72)	0.618
SAPS II at admission	22.59 (5.93)	19.97 (5.24)	0.077
Laboratory test			
White blood cell counts, mean (± SD)	6534.14 (2670.09)	5795.67 (3497.94)	0.367
The number of lymphocytes, mean (± SD)	1018.14 (519.63)	1038.80 (381.86)	0.862
Procalcitonin ng/ml, median (IQR)	0.05 (0.04–0.09)	0.08 (0.05–0.16)	0.181
Lactate dehydrogenase IU/L, mean (± SD)	400.18 (130.73)	325.45 (148.33)	0.049
Troponin-I ng/ml, median (IQR)	9.35 (4.23–14.10)	10.00 (5.10–18.30)	0.783
Treatment			
Remdesivir (%)	13 (44.8)	12 (40.0)	0.911
Antibiotics (%)	29 (100.0)	30 (100.0)	NA
Total accumulative dose of dexamethasone mg, mean (± SD)	62.62 (33.34)	64.17 (32.48)	0.857
Total duration of dexamethasone mg, mean (± SD)	10.66 (5.58)	10.57 (4.48)	0.947
Time interval from symptom onset to dexamethasone administration d, mean (± SD)	7.76 (3.59)	7.03 (3.50)	0.435
Time interval from diagnosis to dexamethasone administration d, mean (± SD)	4.14 (3.26)	4.70 (3.67)	0.537
Clinical outcomes			
High flow nasal cannula or mechanical ventilation (%)	22 (75.9)	12 (40.0)	0.012
Extracorporeal membrane oxygenation (%)	2 (6.9)	0 (0.0)	0.457
Total duration of oxygen supplementation [a, b] d, mean (± SD)	21.61 (16.42)	10.45 (9.39)	0.003
Length of stay in hospital [b] d, mean (± SD)	27.21 (13.28)	19.76 (8.05)	0.013
In-hospital death (%)	1 (3.4)	1 (3.3)	1.000

[a] oxygen supplementation includes oxygen inhalation through nasal prong, facial mask, high flow nasal cannula, mechanical ventilator, and extracorporeal membrane oxygenation.

[b] data regarding total duration of oxygen supplementation and length of stay in hospital were missing for 1 patient in early dexamethasone group and 1 patient in late dexamethasone group.

The continuous variables are expressed as the mean (± standard deviation) or the median (interquartile range) and the categorical variables are expressed as the number of patients (percentage).

IQR, interquartile range; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment

Association between clinical outcomes and the time of dexamethasone administration

Twelve (40.0%) patients in the early dexamethasone group and 22 (75.9%) patients in the late dexamethasone group required HFNC or MV treatment, which was significantly different between the two groups (P-value = 0.012, Table 2). Two patients in the late dexamethasone group were given extracorporeal membrane oxygenation (ECMO) and there was no difference in ECMO use between the two groups. The early dexamethasone group showed a significantly shorter duration of oxygen supplementation (10.45 d *vs.* 21.61 d, P-value = 0.003) and length of stay in hospital (19.76 d *vs.* 27.21 d, P-value = 0.013). We found no difference in in-hospital deaths between the two groups, which were caused in both groups by respiratory failure.

In the univariable logistic regression analysis, early dexamethasone administration was significantly correlated with a lower risk of HFNC or MV treatment (OR = 0.212 [95% CI = 0.069–0.651], P-value = 0.0067, Table 3). In the multivariable logistic regression analysis, the correlation between early dexamethasone administration and a reduced risk of HFNC or MV treatment was statistically significant (model 1, OR = 0.251 [95% CI = 0.080–0.851]; model 2, OR = 0.231 [95% CI = 0.067–0.789]; model 3, OR = 0.153 [95% CI = 0.041–0.578]).

Table 3
Logistic regression analyses to identify the association of time point of dexamethasone administration with high flow nasal cannula or mechanical ventilation

	Univariable analysis		P-Value	Multivariable analysis (model 1)		P-Value	Multivariable analysis (model 2)		P-Value	Multivariable analysis (model 3)		P-Value
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Current smoker	5.143	0.578–45.773	0.142	6.070	0.53–69.534	0.147						
Charlson comorbidity index	1.332	1.028–1.726	0.030	1.335	1.005–1.774	0.046						
SOFA score	1.307	0.869–1.968	0.199				1.145	0.733–1.788	0.551			
SAPS II	1.181	1.057–1.319	0.003				1.153	1.018–1.305	0.025			
The number of lymphocytes	0.999	0.997–0.9999	0.030							0.999	0.997–1.0001	0.073
Remdesivir	5.714	1.731–18.868	0.004							5.967	1.542–23.085	0.010
Early dexamethasone	0.212	0.069–0.651	0.007	0.261	0.080–0.851	0.026	0.231	0.067–0.789	0.019	0.153	0.041–0.578	0.006
The data are expressed as the odds ratio and 95% confidence interval.												
According to rule of thumb, we analyzed three variables in each multivariable logistic regression model.												
In model 1, multivariable logistic regression analysis was adjusted by covariates including current smoker, and Charlson comorbidity index.												
In model 2, multivariable logistic regression analysis was adjusted by covariates including SOFA score and SAPS II.												
In model 3, multivariable logistic regression analysis was adjusted by covariates including lymphocyte counts and remdesivir.												
CI, confidence interval; OR, odds ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment												

In the Kaplan-Meir estimate, the probability of HFNC or MV treatment was significantly lower in the early dexamethasone group (log-rank test = 0.002, Fig. 2). Univariable Cox regression analysis revealed that the probability of HFNC or MV treatment was significantly lower over time in the early dexamethasone group (HR = 0.344 [95% CI = 0.169–0.698], P-value = 0.003, Table 4). In the multivariable Cox regression analysis, early dexamethasone treatment was significantly correlated with a lower rate of HFNC or MV treatment in all three models (model 1, HR = 0.395 [95% CI = 0.192–0.812]; model 2, HR = 0.337 [95% CI = 0.159–0.715]; model 3, HR = 0.339 [95% CI = 0.166–0.690]).

Table 4
Cox regression analyses to evaluate the probability for high flow nasal cannula or mechanical ventilation according to time point of dexamethasone administration

	Univariable analysis		P-Value	Multivariable analysis (model 1)		P-Value	Multivariable analysis (model 2)		P-Value	Multivariable analysis (model 3)		P-Value
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Current smoker	2.448	1.009–5.944	0.048	2.762	1.074–7.104	0.035						
Charlson comorbidity index	1.147	0.977–1.347	0.095	1.154	0.979–1.359	0.087						
SOFA score	1.142	0.955–1.366	0.146				1.123	0.901–1.399	0.301			
SAPS II	1.099	1.031–1.172	0.004				1.073	1.003–1.148	0.040			
The number of lymphocytes	0.999	0.998–0.9999	0.031							0.999	0.998–1.0001	0.088
Remdesivir	2.358	1.184–4.695	0.015							2.065	1.024–4.164	0.043
Early dexamethasone	0.344	0.169–0.698	0.003	0.395	0.192–0.812	0.012	0.337	0.159–0.715	0.005	0.339	0.166–0.690	0.003
The data are expressed as the odds ratio and 95% confidence interval.												
According to rule of thumb, we analyzed three variables in each multivariable cox proportional hazards model.												
In model 1, multivariable cox regression analysis was adjusted by covariates including current smoker, and Charlson comorbidity index.												
In model 2, multivariable dox regression analysis was adjusted by covariates including SOFA score and SAPS II.												
In model 3, multivariable cox regression analysis was adjusted by covariates including lymphocyte counts and remdesivir.												
CI, confidence interval; HR, hazard ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment												

Discussion

Our study identified a correlation between the administration of dexamethasone within 24 hours of oxygen supplementation (early dexamethasone) and a lower rate of HFNC or MV treatment in COVID-19 patients who required oxygen therapy or had a significant desaturation. In addition, the early dexamethasone group showed a significantly shorter total duration of oxygen supplementation and length of stay in hospital. Early dexamethasone treatment was significantly correlated with a lower rate of HFNC or MV treatment, even in multivariable logistic regression analysis and multivariable Cox regression analysis using three models. Although the early dexamethasone group required less HFNC or MV treatment, there was no difference in ECMO use or in-hospital mortality rates between the early and late dexamethasone groups. Therefore, early dexamethasone administration for hypoxemic COVID-19 patients may reduce the need for HFNC or MV treatment without increased mortality; thus, reducing the need for scarce medical resources in the COVID-19 pandemic [11].

Although we know that dexamethasone is associated with a lower mortality rate in COVID-19 patients undergoing oxygen therapy alone [2], information is needed about when dexamethasone treatment should be initiated to maximize the benefits. Considering the evidence to date, the administration of corticosteroids seems to be more effective for COVID-19 patients with active progression to ARDS than those with early-phase pneumonia. In the RECOVERY study, dexamethasone reduced more mortality in the invasive MV group (25.2%; rate ratio = 0.64 [95% CI = 0.51–0.81]), in which pneumonia was more advanced, than the oxygen-only group (37.5%; rate ratio = 0.82 [95% CI = 0.72–0.94]) [2]. In the CoDEX study, dexamethasone benefited COVID-19 patients who used a MV after ARDS developed [3]. A recently published meta-analysis showed that dexamethasone benefits a subgroup of patients with symptom onset > 7

days [1]. The mechanism by which dexamethasone reduces the pulmonary and systematic inflammatory process may contribute to these results [12].

The invasive MV treatment group that received dexamethasone had a higher mortality rate than the oxygen-only group, which did not receive dexamethasone (29.3% *vs.* 26.2%) [2]; therefore, it is not advisable to withhold corticosteroids until HFNC or MV treatment begins. If dexamethasone can prevent the progression from requiring only oxygen supplementation to requiring a MV, it should have a substantial effect in reducing mortality. In RCTs that proved the efficacy of dexamethasone in ARDS, dexamethasone treatment was initiated in the early phase of ARDS (within 48 hours of onset) [3, 7]. This suggests that suppression of pathological inflammation by controlling macrophage activation and cytokine release in the early phase of ARDS may be important for a positive outcome [13].

In our study, the number of patients in the early and late dexamethasone treatment groups was almost the same, which reflects the controversy in clinical practice concerning the optimum time for dexamethasone administration. In the late dexamethasone group, it is likely that the physician did not expect the oxygen demand of the patient to increase; thus, dexamethasone would not have been be prescribed immediately. In fact, before studies on mortality reduction by dexamethasone were published, we had COVID-19 pneumonia cases where the oxygen demand gradually decreased without dexamethasone [14]. However, there is still no good tool to predict whether COVID-19 pneumonia will worsen. Serious adverse events were no different between patients treated or not treated with dexamethasone, while the benefit of dexamethasone was significant only in the oxygen group [1, 2]. In our study, dexamethasone treatment within 24 hours of oxygen supplementation decreased the need for HFNC or MV interventions. The mean time from symptom onset to dexamethasone treatment was about 7.4 days. Therefore, when oxygen supplementation is needed, especially after 7 days of symptom onset, prompt administration of dexamethasone may be advantageous.

The present study has several limitations. First, this study was a retrospective observational study with a small number of patients. To control for confounding variables, we conducted multivariable analyses with three models. Second, the early dexamethasone group may have included more patients with less severe COVID-19 pneumonia, although there was no difference in SOFA scores and SAPS II between the early and late dexamethasone groups. The late dexamethasone group received dexamethasone only after progression of hypoxemia, whereas in the early group dexamethasone was administered as soon as hypoxemia occurred. Therefore, the patients with a milder disease, who improved without dexamethasone, may not have been included in the late dexamethasone group, but would have been included in the early dexamethasone group. Third, our study did not include very severe cases with rapid progression to ARDS. We excluded three patients who had severe hypoxemia at admission and needed HFNC treatment immediately, before dexamethasone was started. Although the anti-inflammatory effect of dexamethasone is likely to be most pronounced in ARDS patients with rapid progression, our results cannot be extrapolated to these patients. Fourth, the early and late dexamethasone groups had similar rates of remdesivir treatment; however, the timing of remdesivir administration was as late as that of dexamethasone in the late dexamethasone group.

Conclusions

The administration of dexamethasone within 24 hours of oxygen supplementation correlated with a lower rate of HFNC or MV treatment in patients with severe COVID-19 pneumonia. The duration of oxygen supplementation and length of hospital stay were shorter in the early dexamethasone treatment group. Early administration of dexamethasone may also be beneficial in the prevention of ARDS progression and may prevent the need for HFNC or MV treatment, without an increase in fatal events.

Abbreviations

ARDS, acute respiratory distress syndrome; BMI, body mass index; CCI, Charlson comorbidity index; CIs, confidence intervals; COVID-19, coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; HRs, hazard ratios; IQR, interquartile range; ORs, odds ratios; qRT-PCR, real-time reverse transcription-polymerase chain reaction; RCTs, randomized controlled trials; RR, rate ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; SpO2, pulse oximeter oxygen saturation

Declarations

Ethical Approval and Consent to participate

The Institutional Review Board Committee of Seoul National University Hospital approved the study protocol and waived the need for informed consent for access to the electronic medical records (IRB No. 20-2020-33).

Consent for publication

Not applicable

Availability of supporting data

All relevant data are available upon request from the corresponding author.

Competing interests

The authors declare no support from any organization for the submitted work, no financial relationship with any organization that might have an interest in the submitted work within the previous 3 years, and no other relationship or activity that could appear to have influenced the submitted work.

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Author contributions

Study concept and design: HWL, EYH

Acquisition of data: HWL, EYH

Analysis and interpretation of data: HWL, EYH

Drafting the manuscript: HWL

Critical revision of the manuscript and important intellectual content: JMP, JKL, TYP, EYH

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Not applicable

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Figures

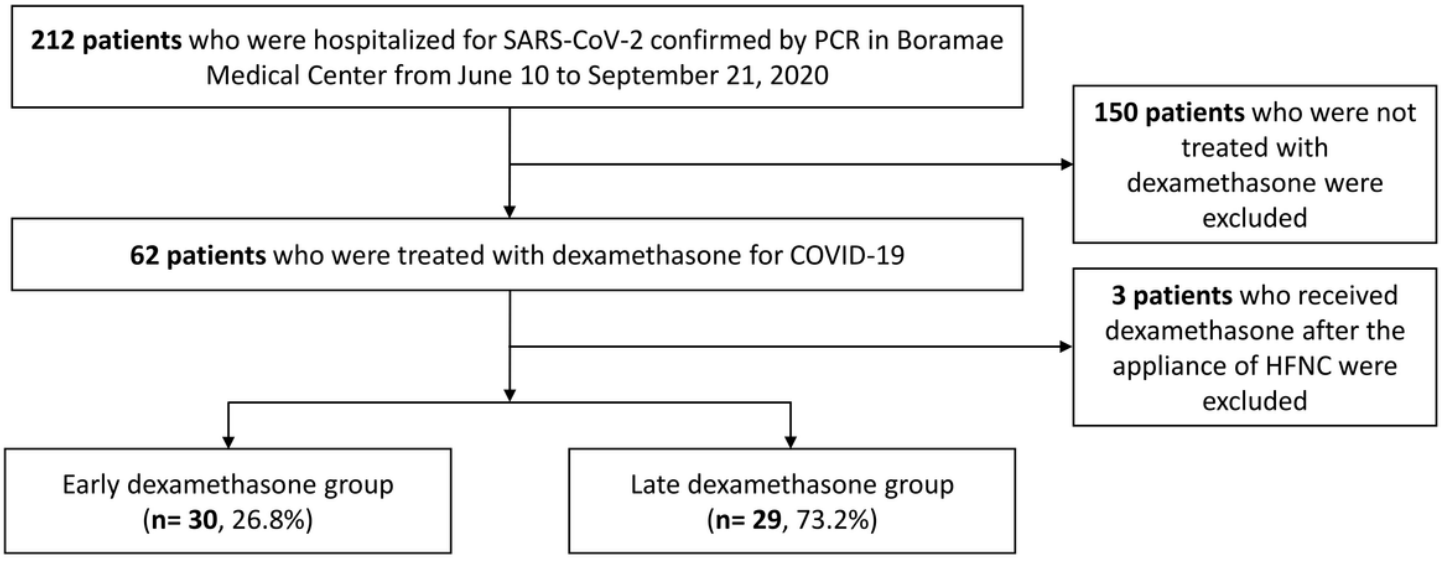
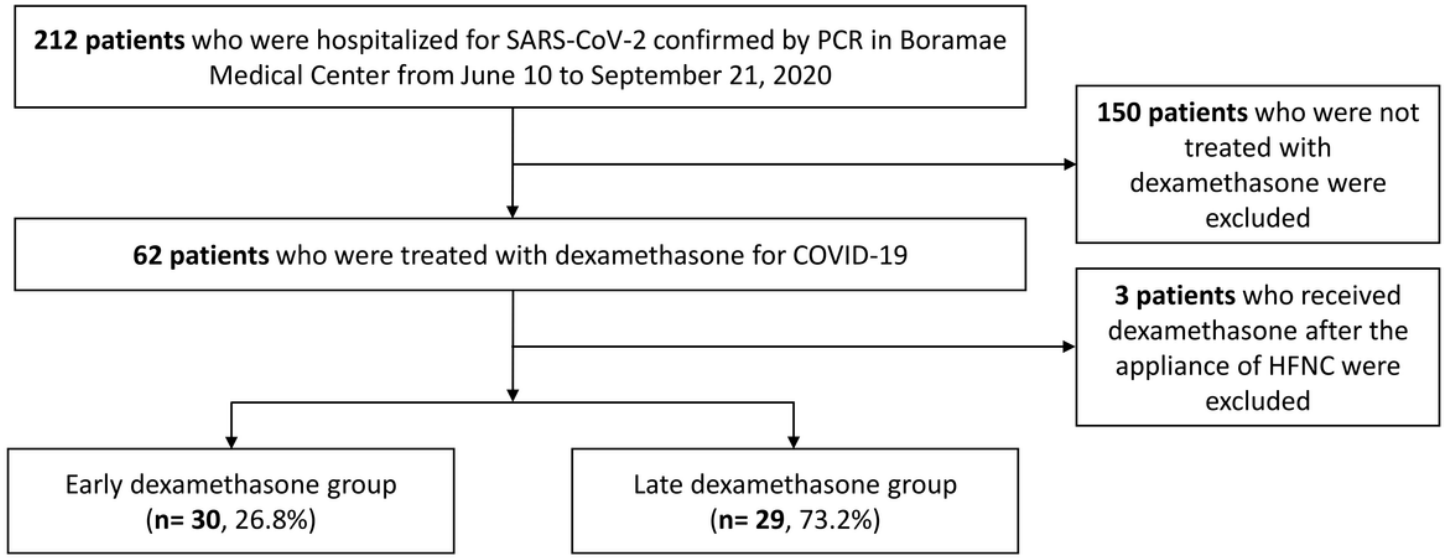


Figure 1

Flow chart of patient inclusion PCR, polymerase chain reaction; COVID-19, coronavirus disease 2019



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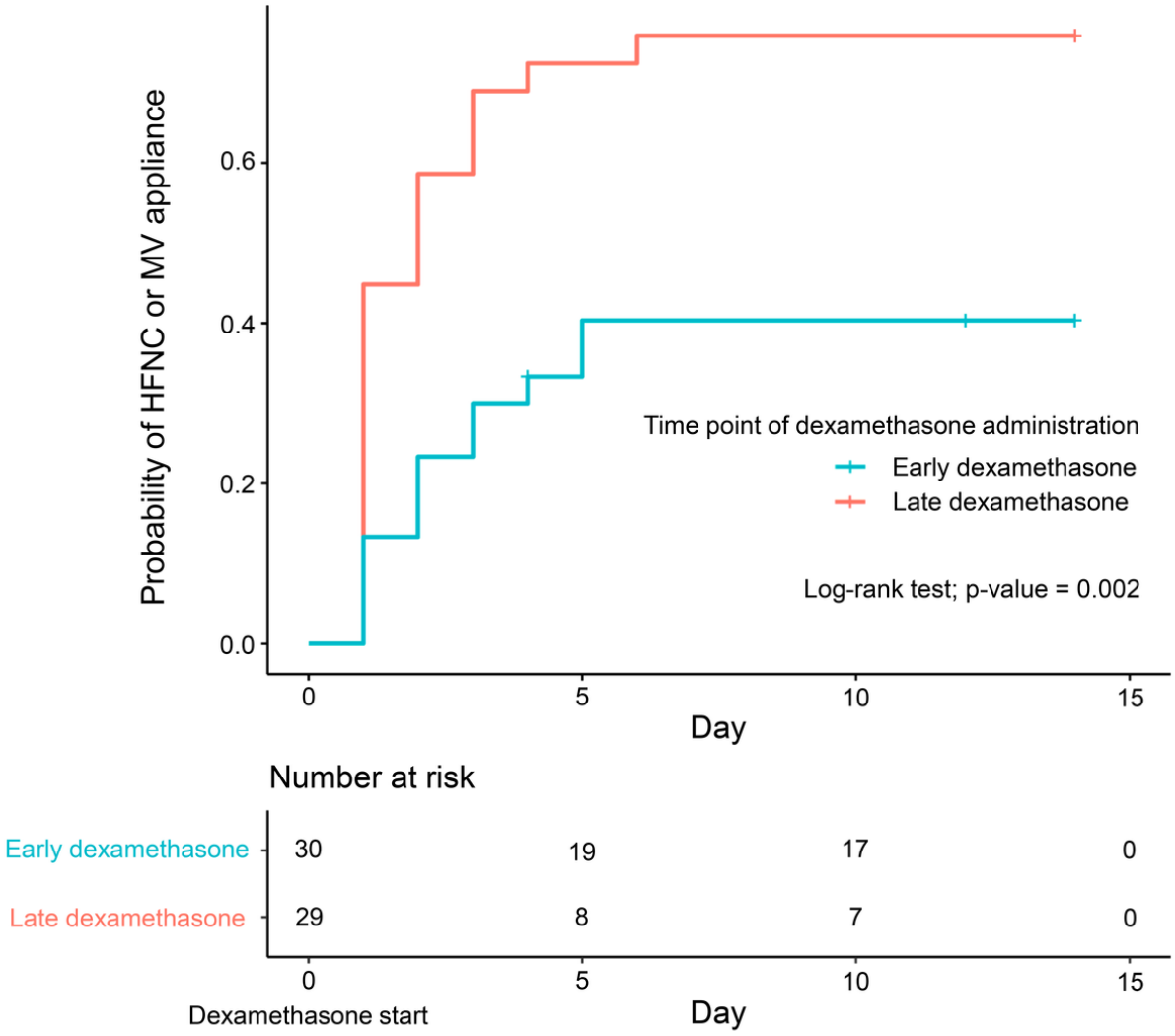
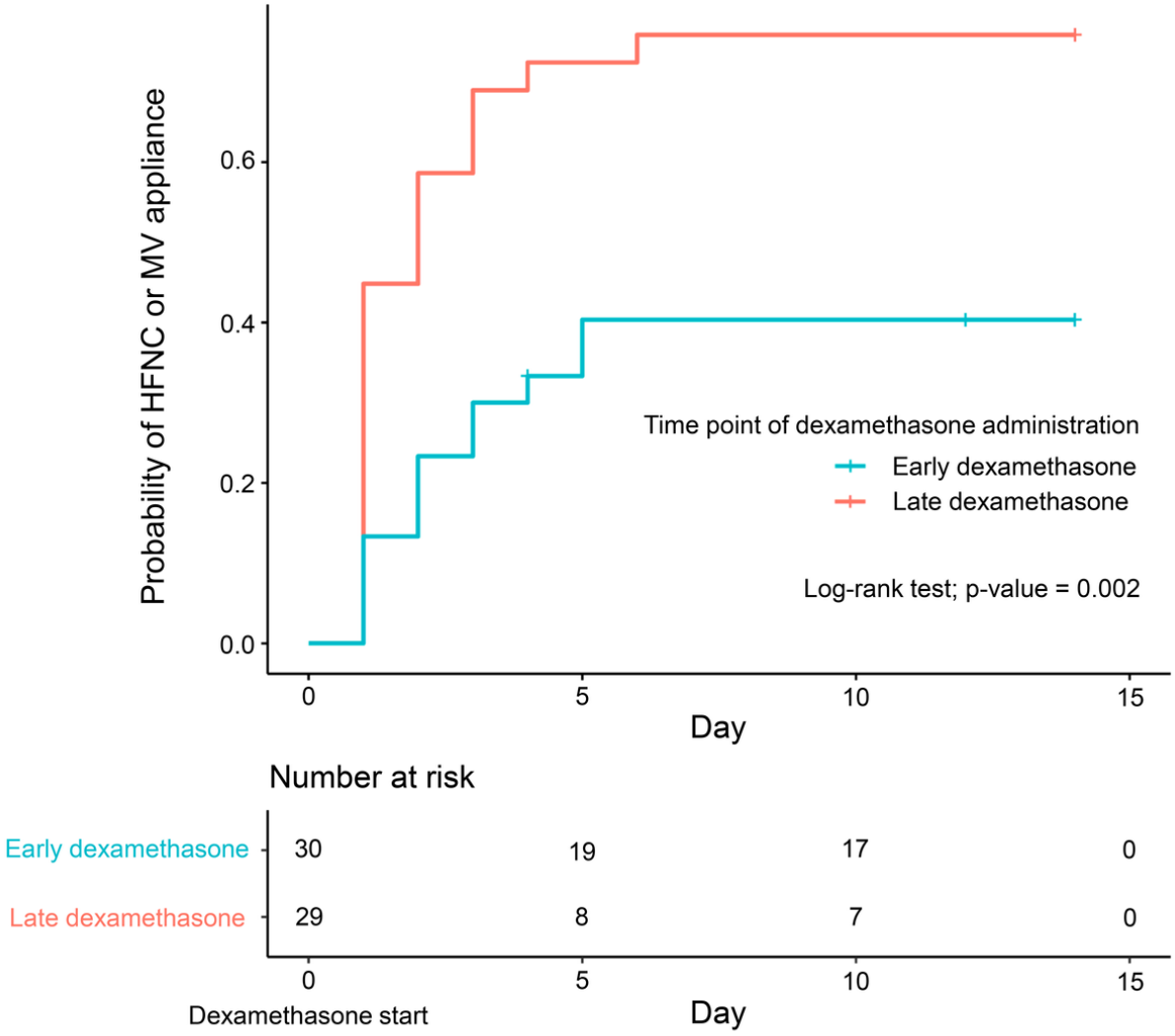


Figure 2

Kaplan–Meier curve for probability of HFNC or MV treatment for 2 weeks after the initiation of dexamethasone administration HFNC, high-flow nasal cannula; MV, mechanical ventilator



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