

Early Versus Late Use of Dexamethasone in Critically Ill Patients With COVID-19: A Multicenter, Prospective Cohort Study

Khalid Al Sulaiman (✉ alsulaimankh@hotmail.com)

King Abdulaziz Medical City <https://orcid.org/0000-0002-5547-2043>

Alaa Alhubaishi

Princess Nora bint Abdulrahman University College of Pharmacy

Ohoud Al Juhani

King Abdulaziz University

Khalid Eljaaly

King Abdulaziz University

Omar Al Harbi

King Abdulaziz Medical City

Hisham A. Badreldin

King Saud bin Abdulaziz University for Health Sciences College of Pharmacy

Ghada Al Yousif

King Abdulaziz Medical City

Ramesh Vishwakarma

King Abdullah International Medical Research Center

Shorouq Albelwi

Princess Nora bint Abdulrahman University College of Pharmacy

Rahaf Almutairi

Princess Nora bint Abdulrahman University College of Pharmacy

Maha Almousa

Princess Nora bint Abdulrahman University College of Pharmacy

Razan Alghamdi

Princess Nora bint Abdulrahman University College of Pharmacy

Aisha Alharbi

King Abdulaziz University Hospital

Rahmah Algarni

King Abdulaziz University Hospital

Nada Akhani

King Fahad Medical City

Abdulaleam Al Atassi

King Abdulaziz Medical City

Ghassan Al Ghamdi

King Abdulaziz Medical City

Research

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Abstract

Background:

Corticosteroids, especially dexamethasone, showed a survival benefit in critically ill COVID 19 patients. However, it is unclear whether the timing of dexamethasone initiation is associated with positive outcomes. The aim of this study is to evaluate the timing of dexamethasone initiation and 30-day mortality in critically ill patients with COVID19.

Methods:

A multicenter, non-interventional, prospective study for all adult COVID19 patients admitted to intensive care units (ICUs) received systemic dexamethasone between March 01 to December 31, 2020. Patients were divided into two groups based on the timing for dexamethasone use (early vs. late). Early use is defined as new initiation of dexamethasone within three days of ICU admission or initiation prior to ICU admission (e.g., wards) and continuation during ICU stay. Propensity score matching was used after adjusting for patient's age, gender, and mechanical ventilation needs within 24 hours of ICU admission. We considered a P value of < 0.05 statistically significant.

Results:

A total of 475 patients were included in the study; dexamethasone was used early within three days of ICU admission in 435 patients. Among 156 patients matched using propensity score, 39 had received dexamethasone after three days of ICU admission (Ratio 1:4). 30-day mortality (OR [95%CI]: 1.86[0.87, 3.95], p-value=0.11) and in-hospital mortality (OR [95%CI]: 1.47[0.71, 3.06], p-value=0.29) were not statistically significant between the two groups. Early use of dexamethasone was associated with shorter MV duration (beta coefficient [95% CI]: -0.67 [-1.31, -0.04], p-value=0.04), ICU length of stay (LOS) (beta coefficient [95%CI]: -0.66 [-0.961, -0.36], p-value=0.001), and hospital LOS (beta coefficient [95%CI]: -0.65 [-0.92, -0.39], p-value=0.001).

Conclusion:

Early use of dexamethasone within three days of ICU admission in COVID-19 critically ill patients was associated with shorter MV duration, ICU and hospital LOS.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in 2019. Coronaviruses (CoVs) are ribonucleic acid (RNA), positive-stranded viruses with nucleocapsid, which can spread rapidly.^{1,2} The mortality rate reported is around 40% in critically ill patients with comorbidities who were infected with SARS-CoV-2.^{3,4}

Severe COVID-19 disease can enhance the systematic inflammatory response in critically ill patients, causing a systemic hyperinflammatory state, leading to multiple complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and thrombosis, which can increase mortality rate^{4,5,6}. To date, there are limited therapeutic options showing a positive impact for reducing the complications secondary to COVID-19 infection.⁷

Patients with moderate to severe COVID-19 are treated with antiviral medications, anti-inflammatory /antirheumatic drugs, plasma, and hyperimmune immunoglobulins. Treating with systematic corticosteroids was a debate, but the fact that COVID-19 patients can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction made this class a potential therapeutic option.^{8,9} It has been proposed that the potent anti-inflammatory mechanism of corticosteroids might prevent or mitigate these deleterious effects.¹⁰

RECOVERY trial, a multicenter, randomized, open-label trial performed in the United Kingdom, showed that a significant mortality reduction at 28-days in hospitalized patients who received dexamethasone for up to 10 days compared to patients who received the standard of care.^{10,29} This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment²⁹. Moreover, 44 studies have used a variety of corticosteroid strategies in COVID-19 patients.^{11,12} The most used corticosteroid in these studies was methylprednisolone, while the least used were prednisone, dexamethasone, and hydrocortisone. The outcomes varied between studies; some reported longer hospital stay in the corticosteroid group, and others reported the opposite or no effect on hospital stay. Many studies reported a positive effect of corticosteroids on ventilator-free days, the number of patients requiring mechanical ventilation for respiratory failure, and the mechanical ventilator timing^{11,12,13,29}.

However, the appropriate timing for corticosteroids initiation in critically ill patients with COVID19 remains to be answered. There is limited and unclear data regarding corticosteroid initiation's appropriate timing, especially dexamethasone in COVID19 critically ill patients. This study aims to evaluate the proper timing of systemic dexamethasone initiation in critically ill patients with COVID19 and its clinical outcomes.

Methods

Study design

This is a multicenter, non-interventional, prospective study in critically ill patients aged > 18-years with COVID19 (diagnosed according to reverse transcriptase-polymerase chain reaction (RT-PCR) obtained from nasopharyngeal or throat swabs), who were admitted to the ICU at two tertiary hospitals in Saudi Arabia from March 01, 2020, until December 31, 2020. We aimed to enroll as many patients as possible, with no predefined sample size. Patients were excluded if they did not receive corticosteroid therapy during the ICU period or labeled as "Do-Not-Resuscitate" code status within 24 hours of ICU admission.

Participants

Eligible patients were classified into two groups based on the timing of dexamethasone initiation during ICU stay (early vs. late initiation). The definition of early versus late corticosteroids initiation is debatable in critically ill patients in general and, more specifically, in COVID19 patients. We decided to choose three days cutoff margin for early vs. late initiation definition based on clinical judgment. It is well known that COVID19 related lung injury and its associated hyperinflammatory and overreacting immune response occur early in ARDS presentation. In our study, early initiation was defined as systemic dexamethasone initiation before ICU admission (e.g., wards) and continuation during ICU stay or newly initiated within three days of ICU admission, whereas late initiation was defined as dexamethasone after three ICU admission days. All included patients have received a dose of 6 mg IV once daily of dexamethasone or its equivalent based on the national protocol of the ministry of health (MOH) in Saudi Arabia¹⁴. Patients were followed during ICU stay. The study was approved by King Abdullah International Medical Research Center in July 2020 (Ref.# RC20/430/R).

Setting

This study was conducted in two tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh, and King Abdulaziz University Hospital, Jeddah. The primary site for this multicenter study was King Abdulaziz Medical City (Riyadh).

Data collection

We collected demographic data (See additional file 1), comorbidities, vital signs and laboratory tests, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Nutrition Risk in Critically ill (*NUTRIC*) scores, Glasgow Coma Score (GCS), acute kidney injury, fluid balance, the needs for mechanical ventilation (MV) and MV parameters (e.g., PaO₂/FiO₂ ratio, FiO₂ requirement) within 24 hours of ICU admission. Also, renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen), and inflammatory markers (CRP, procalcitonin) within 24 hours of ICU admission were collected. Tocilizumab use was recorded for the eligible patients. All patients were followed until they were discharged from the hospital or died during the in-hospital stay, whichever occurred first.

Outcomes

The primary endpoint was to evaluate the timing of dexamethasone initiation and its association with 30-day mortality in critically ill patients with COVID 19. The secondary endpoints were to assess the in-hospital mortality, hospital LOS, ICU LOS, MV duration, and, ICU-related complication (s) during ICU stay (i.e., acute kidney injury (AKI), liver injury, respiratory failure requires MV, thrombosis/infarction).

Definition (s)

- Acute kidney injury (AKI) was defined using Acute Kidney Injury Network (AKIN) definition¹⁵.
- Thrombosis/infarction was defined using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) code (i.e., myocardial infarction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) during ICU stay¹⁶.
- Respiratory failure was defined as either hypoxemic respiratory failure ($\text{PaO}_2 < 60$ mm Hg with a normal or low arterial carbon dioxide tension (PaCO_2) or hypercapnic respiratory failure ($\text{PaCO}_2 > 50$ mm Hg) that requires mechanical ventilation.
- Acute liver injury was defined as alanine aminotransferase (ALT) exceeding three times the upper limit of normal or double in patients with elevated baseline ALT during the hospital stay.

Data management and Statistical analysis

We presented categorical variables as number (percentage), numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate. The normality assumptions were assessed for all numerical variables using a statistical test (i.e., Shapiro–Wilk test) and graphical representation (i.e., histograms and Q-Q plots). We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection.

We compared categorical variables using the Chi-square or Fisher exact test. We compared the normally distributed continuous variables using student t-test and other non-normally distributed continuous variables with the Mann-Whitney U test. Baseline characteristics, baseline severity, and outcome variables were compared between the two groups. Multivariate logistic and generalized linear regression were used to find out the relationship between the timing of initiation with different outcomes considered in this study after adjusting for patient's age, gender, and mechanical ventilation needs within 24 hours of ICU admission⁴. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. We considered a P value of < 0.05 statistically significant, and we used SAS version 9.4 for all statistical analyses.

Propensity score matching Procedure (Proc PS match) (SAS, Cary, NC) with a 1: 4 ratio were used to match patients in the late group to early Dexamethasone group. A greedy nearest neighbor matching method was used in which one late use of dexamethasone (control) is matched with four patients in the early use of dexamethasone (treated) group; this eventually produces the smallest within-pair difference among all available pairs with treated patients. These patients are matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups is less than or equal to 0.5 times the pooled estimate of the standard deviation.

Results

Demographic and Clinical Characteristics

A total of 758 critically ill patients with COVID-19 were screened, 475 patients with COVID19 have received dexamethasone during the study period. Out of the 475 patients, 91.5 % (435 patients) received dexamethasone early before ICU admission and continued during ICU stay or newly initiated within three days of ICU admission. A total of 156 patients were included after propensity score matching using the patient's age, gender, and mechanical ventilation needs within 24 hours of ICU admission. The majority of the patients were men (87.2%), and the mean age of the patients was 58.8 ± 13.2 years (Table 1, Supplemental Digital Content 1). The most common comorbidities were diabetes mellitus (62.4%), hypertension (53.1%), and dyslipidemia (21.9%); comorbidities were not significantly different between the two groups (Table 2, Supplemental Digital Content 2).

The baseline severity scores (i.e., APACHE II, SOFA, and NUTRIC scores), Glasgow coma score (GCS), lactic acid, platelets count, CRP, CPK, ferritin, procalcitonin, $\text{PaO}_2/\text{FiO}_2$ ratio, and acute kidney injury within 24 hours of ICU admission, were not significantly different between the two groups. The median APACHE II score was 12, while the median SOFA score was 5. Two-thirds of patients needed MV within 24 hours of ICU admission. Additionally, the difference in tocilizumab use during ICU stay was not significant between the two groups (Table 1, Supplemental Digital Content 1).

Mortality and length of stay

ICU mortality within 30 days in early groups was 46.1% compared with 31.6 % in the late initiation after using propensity score matching adjusted for patient's age, gender, and mechanical ventilation needs within 24 hours of ICU admission (OR [95%CI]: 1.86 [0.87, 3.95], p-value=0.11) (Table 1).

Among survived patients who received dexamethasone early, we observed a significant shorter hospital length of stay (beta coefficient [95%CI]: -0.65 [-0.92, -0.39], p-value=0.001), ICU LOS (beta coefficient [95%CI]: -0.66 [-0.961, -0.36], p-value=0.001), and MV duration (beta coefficient [95% CI]: -0.67 [-1.31, -0.04], p-value=0.04) compared to the late initiation of dexamethasone (Table 1).

ICU Complications during ICU stay

Critically ill patients with COVID19 who received early dexamethasone have a lower risk for developing respiratory failure (OR (95%CI): 0.55 (0.13 ,2.23), p-value=0.41), acute kidney injury (OR (95%CI): 0.70 (0.34, 1.46), p-value=0.35), and thrombosis during ICU stay (OR (95%CI): 0.60 (0.23 ,1.57), p-value=0.30); however, it was not statistically significant, as shown in Table 1.

Discussion

Our study aimed to evaluate the effect of dexamethasone initiation time on critically ill COVID19 patients' clinical outcomes. A total of 475 patients were included in the analysis; dexamethasone was initiated early in the majority of the included 435 (91.5%) patients. The study took place from March 2020 before the reslaese of RECOVERY trial results, clinicansce were hesitant to start dexamethasone early in some patients at that time and this translated in 8.4% of our included patients being in the late group. After

propensity score matching using the patient's age, gender, and mechanical ventilation needs within 24 hours of ICU admission, we found that dexamethasone early initiation was associated with shorter hospital LOS, ICU LOS, and MV duration among survived patients.

The clinical presentation of COVID19 ranges in severity from asymptomatic mild disease to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) and associated with a high mortality rate^{17,18}. In critically ill COVID19 patients, the clinical presentation of ARDS, massive vascular inflammation, disseminated intravascular coagulation, and shock is triggered frequently, with an ARDS occurrence rate of 17% to 41% of all cases^{19,20}. The dysregulated inflammatory immune response observed with COVID19 is similar to multifactorial ARDS, where plenty of evidence has proven corticosteroids ability to down-regulate the inflammatory immune response and accelerate disease resolution^{21,22,23}. Although the World Health Organization (WHO) initially did not recommend using corticosteroids for COVID19 treatment, as of September 02, 2020, the WHO recommended using systemic corticosteroids in critically ill patients with severe COVID19 over no use²⁴. Furthermore, the surviving sepsis guideline recommends steroid administration in severe COVID19 cases with ADRS requiring MV and patients with refractory shock²⁵.

In our study, early dexamethasone initiation was not associated with a significant reduction in 30-day mortality (OR [95%CI]: 1.86 [0.87, 3.95], p-value=0.11). Our findings of no mortality differences between the groups might be limited by including patients who received dexamethasone prior to ICU admission where they might have less severe ARDS and the mortality benefits in this group is not well documented. The well known RCT (RECOVERY trial) concluded that the use of dexamethasone regardless of timing was associated with lower 28-day mortality among patients who received respiratory support¹⁰. A recent systematic review and meta-analysis compared the effect of corticosteroids versus standard of care; the study suggested that corticosteroids were associated with a significant reduction in the mortality rates in COVID-19 patients²⁶. Furthermore, another meta-analysis by Sterne et al., that included data from seven randomized clinical trials aimed to evaluate the association between corticosteroids administration and 28-day all-cause mortality reported that corticosteroids associated with lower mortality rates compared with standard of care²⁷. However, none of these meta-analyses included studies that assessed the association between the corticosteroids, specifically dexamethasone initiation time and mortality benefits. Currently, majority of treatment guidelines recommend to start corticosteroids in severe or critical ill COVID19, however no clear recommendation regarding the timing or mild to moderate COVID19 patients²⁵.

The present study found shorter hospital length of stay (LOS), ICU LOS, and MV duration in the early group compared to the late group of dexamethasone. In parallel to our findings, a recent prospective study by Monedero et al. compared outcomes between patients who received either early, delayed, or not received corticosteroids. They found that early corticosteroids use in critically ill COVID19 patients associated with shorter MV duration and less ICU LOS²⁸. In our study, the two groups have similar baseline characteristics with a defined cutoff margin of corticosteroid initiation time based on the ICU

admission timeframe. Moreover, we only included patients who received dexamethasone to have a consistent comparison with the RECOVERY trial¹⁰. However, RECOVERY trial did not investigate if early dexamethasone initiation is different from just initiating dexamethasone at any given point in terms of hospital length of stay (LOS), ICU LOS, and MV duration. .

In terms of ICU complications during ICU stay, our study found that early initiation of dexamethasone was associated with a lower incidence of acute kidney injury, respiratory failure and thrombosis but did not reach to statistically significant difference. That could be related to dexamethasone's prolonged and potent effect which can mediate downregulation of systemic and pulmonary inflammation, restore homeostasis, and enhance disease resolution. In comparison to our findings, Monedero et al²⁸ reported a lower rate of acute renal failure in the early group. and a lower rate of mechanical ventilation in the early steroids group. This could be justified by starting dexamethasone in less severe patients in the medical floor prior to ICU admission which was limited to control due to the observational nature of our study.

We believe that our multicenter prospective cohort study is the first study that highlights the appropriate time of dexamethasone initiation and its effects on critically ill COVID19 patients' clinical outcomes. It is prospective design allows to prospectively explore the association between the time of dexamethasone therapy initiation in COVID19 patients with ICU mortality. Additionally, it had a predefined cutoff margin of early vs. late initiation time, and it assessed several important clinical outcomes in the final analysis. Nevertheless, we also determined some limitations to our study. First, the observational nature of the study design and some residual confounding factors are still possible and timing of early steroids was not controlled prior to ICU admission. Second, this study only focused on the ICU-related outcomes, but the safety outcomes and steroids-related side effects need to be addressed in further studies. Third, we cannot exclude missing data for some variables due to the observational design. Lastly, there was a dynamic change in the national and international COVID19 management guidelines as more evidence continued to emerge, which affected the general practice.

Conclusion

Our multicenter, prospective cohort study showed that early use of dexamethasone within three days of ICU admission in COVID19 critically ill patients was associated with shorter MV duration, ICU and hospital LOS but no difference in the mortality benefit. Further randomized clinical and interventional studies are needed to confirm our findings.

Declarations

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Not applicable.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved in July, 2020 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/430/R).

Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the policy of the governmental and local research center.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

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Tables

Table 1: Co-existing illness

Existing illness	Overall (475)	Early (N=435)	Late (N=40)	P-value
Anemia, n (%)	115 (24.4)	109 (25.2)	6 (15.4)	0.17^^
Diabetes mellitus, n (%)	300 (63.7)	275 (63.7)	25 (64.1)	0.96^^
Hypertension, n (%)	273 (58.0)	252 (58.3)	21 (53.8)	0.59^^
Coronary syndrome (ACS), n (%)	4 (0.9)	4 (0.9)	0 (0.0)	>0.99**
Stroke, n (%)	38 (8.1)	37 (8.6)	1 (2.6)	0.35**
Arrhythmia, n (%)	15 (3.2)	13 (3.0)	2 (5.1)	0.36**
Chronic obstructive pulmonary disease, n (%)	9 (1.9)	9 (2.1)	0 (0.0)	>0.99**
Heart failure, n (%)	21 (4.5)	19 (4.4)	2 (5.3)	0.69**
Chronic kidney disease- (Non-Dialysis), n (%)	35 (7.4)	31 (7.1)	4 (10)	0.80**
Chronic kidney disease- (On Dialysis) n (%)	16 (3.4)	15 (3.5)	1 (2.6)	
Coronary artery bypass grafting, n (%)	12 (2.6)	11 (2.6)	1 (2.6)	>0.99**
Renal failure, n (%)	32 (6.8)	31 (7.2)	1 (2.6)	0.50**
Hyperthyroidism, n (%)	30 (6.4)	28 (6.5)	2 (5.1)	>0.99**
Ischemic heart disease, n (%)	42 (9.0)	39 (9.1)	3 (7.7)	>0.99**
Seizure, n (%)	11 (2.4)	10 (2.3)	1 (2.6)	>0.99**

Denominator of the percentage is the total number of patients
 NS = Not Significant / ** Fisher's Exact test is used to calculate P-value.

Table 2: Regression analysis for the outcomes

Outcomes	Dexamethasone				
	Early	Late	P value	Odds Ratio (OR) (95%CI)	P-value
7 ICU mortality, n (%)	166/421 (39.4%)	12/39 (30.7%)	0.29 ^{^^}	0.43 (0.231,0.813)	0.01* [^]
30-day mortality, n (%)	197/428 (46%)	16/39 (41%)	0.55 ^{^^}	0.60 (0.294 ,1.227)	0.16* [^]
ICU admission within 3 months, n	26/334 (7.8)	2/32 (6.3)	>0.99**	1.10 (0.244, 4.962)	0.90* [^]
Acute kidney injury during ICU stay, n (%)	210/433 (48.4)	25/40 (62.5)	0.09 ^{^^}	0.45 (0.215, 0.940)	0.03* [^]
Acute kidney injury during ICU stay, n (%)	54/433 (12.4%)	3/40 (7.5%)	0.45**	1.68 (0.493 ,5.794)	0.40* [^]
Respiratory failure required MV during ICU stay, n (%)	318/433 (73.4%)	34/40 (85%)	0.11 ^{^^}	0.56 (0.147, 2.093)	0.38* [^]
Respiratory failure during ICU stay, n (%)	39/429 (9%)	7/40 (17.5%)	0.09**	0.44 (0.18 ,1.073)	0.07* [^]
				beta coefficient (Estimates) (95%CI)	P-value
Duration during ICU (days), n (Q1, Q3) &	3.5 (1.00, 11.00)	13.0 (8.50, 22.00)	<0.001 [^]	-0.94(-1.477,-0.395)	<0.001** [^]
Total length of stay (days), n (Q1, Q3) &	16.0 (11.00, 24.00)	34.0 (28.00, 45.00)	<0.001 [^]	-0.68 (-0.913, -0.452)	<0.001** [^]
Length of Stay (days), Median (Q3) &	8.0 (5.00, 13.00)	22.0 (17.0, 28.00)	<0.001 [^]	-0.73 (-0.9971, -0.469)	<0.001** [^]

Denominator of the percentage is the total number of patients
 Fisher's exact test is used to calculate the P-value.
 Chi-square test is used to calculate the P-value.
 Fisher's Exact test is used to calculate the P-value.

Univariate Logistic regression is used to calculate p-value after adjusting for patient's age, the needs of MV within 24 hours of ICU admission, and hospital center.

Generalized linear regression is used to calculate p-value after adjusting for patient's age, the needs of MV within 24 hours of ICU admission, and hospital center.

Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.

Denominator is patients who survived.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1Table1.docx](#)
- [Additionalfile2Table2.docx](#)