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Brief Report

High-Dose vs. Low-Dose Dexamethasone in Patients With COVID-19: A Cohort Study in Rural Central America

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To compare the clinical outcomes of a low dose dexamethasone strategy vs. a high-dose dexamethasone strategy in hypoxemic COVID-19 patients. A retrospective observational study comparing low-dose (8 mg) and high-dose dexamethasone (24 mg) of COVID-19 patients admitted from September 1, 2020 to October 31, 2020 in a hospital in Honduras. We included 81 patients with confirmed COVID-19 who required oxygen therapy. The mean age was similar between groups (57.49 vs. 56.95 years). There were more male patients in the group of 24 mg (p = 0.01). Besides, patients on the 24 mg dose had more prevalence of hypertension (p = 0.052). More patients in the 24 mg group had a higher rate of invasive mechanical ventilation (15.00% vs. 2.56%, p = 0.058). When evaluating the association between the high dose group and outcomes, we find no significant association with mortality, nosocomial infections, high flow mask, invasive mechanical ventilation, or the need for vasopressors. We find no significant differences in the Kaplan–Meier analysis regarding the survival (log-rank p-value = 0.315). We did not find significant differences between the use of 24 mg and 8 mg of dexamethasone in hypoxemic COVID-19 patients.

Keywords: *COVID-19, corticosteroids, Western Honduras, Latin America, cohort, Latinos or Hispanic*

Introduction

The coronavirus disease 2019 (COVID-19) can cause viral pneumonia, which may progress to acute respiratory distress syndrome, which is driven by a hyperinflammatory state. The cornerstone of therapy against the severe forms of COVID-19 is therapeutics targeted at reducing this inflammation and cytokine storm.[1,2]

Corticosteroids were the first medications that were found to help reduce mortality in those patients with COVID-19 who required oxygen. The landmark trial found that dexamethasone at 6 mg per day for 10 days was associated with decreased mortality compared to usual care.[1] Prior to the RECOVERY trial, Villar et al.[3] had already found dexamethasone to improve outcomes in patients with acute respiratory distress syndrome but at a much higher dose of 20 mg

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daily for five days, followed by 10 mg by another five days.

To ameliorate the cytokine storm, dexamethasone has become the standard of care for hypoxemic COVID-19 patients, coupled with either interleukin-6 inhibitors or Janus kinase 2 (JAK2) inhibitors.[4,5] However, the role of dexamethasone has not been clearly established in the question of whether a low-dose strategy (i.e., dexamethasone at 6 mg/day) is superior to a high-dose strategy (i.e., dexamethasone at 20 mg/day), especially in those who develop a critical illness.[6]

We designed a retrospective cohort study in Western rural Honduras, the first and only study in low-and middle-income countries setting from Latin America that aims to compare a low-dose vs. high-dose strategy and evaluate if there was a difference between these two approaches.

Methods

Study Design and Patients

We performed a retrospective cohort study of hypoxemic patients with COVID-19 admitted to a Western Honduran hospital between 09/02/2020 to 10/31/2020. Patients who were > 18 years of age had confirmed SARS-CoV2 (with PCR) and who required at least 10 L of oxygen therapy or mechanical ventilation for severe hypoxemia. We excluded patients using corticosteroids for indications other than COVID-19, or that received steroids prior to arrival to the hospital. The Ethics Committee of Western Honduras Hospital (Institutional Review Board) approved the study on July 27, 2021 (code: IORG0009835; ID approval 11680). It was conducted in compliance with local regulations and requirements, Good Clinical Practice, and the Declaration of Helsinki.

Procedure

All patients admitted received the standard of care established by the Honduran health authorities for COVID-19. The dexamethasone dose depended on the time of patient admission rather than illness severity. In Honduras, the shifts are divided into three: (1) morning shift from 7:00 am to 1:00 pm, (2) afternoon shift from 1:00 pm to 7:00 pm, and (3) night shift, a 12-hour shift to complete the 24 hours coverage. Patients who came between 7:00 am to 1:00 pm were assigned to the low-dose (8 mg) dexamethasone arm. Those who arrived between 1:00 pm to 7:00 pm were assigned to the high-dose (24 mg) arm. The night team admission was not included in the study. Dexamethasone was given for a total of 10 days.

The doses were chosen like this because the only presentation of dexamethasone available is 8 mg per vial of the drug. This administration pattern did not depend on the symptoms or respiratory failure severity. The head physician of the COVID-19 unit determined this: the head staff in the morning preferred lower doses of dexamethasone, and the head staff in the afternoon chose the high dose of dexamethasone for COVID-19. At the moment of the study, non-inferiority trials of the doses of steroids have been published in the medical literature. In Honduras, dexamethasone vials only come in 8 mg; therefore, national policy and standard of care were to administer 8 mg of dexamethasone as opposed to the 6 mg of dexamethasone dose utilized in the RECOVERY trial.[1]

Baseline information was collected on hospital admission: demographic features, underlying diseases, oxygen saturation, respiratory rate, C-reactive protein, complete blood count, and erythrocyte sedimentation rate (blood drawn within two hours of arrival to the emergency department). We followed the patients' outcomes up to day 28.

Outcomes

The primary outcome was mortality. The secondary outcomes were nosocomial infections, the need for a high flow oxygen therapy, invasive mechanical ventilation, or the need for vasopressors.

Statistical Analysis

We used the percentage for qualitative variables. We used the mean or median to express the information of a quantitative variable according to its distribution. The histogram evaluated the distribution. The Chi-square test compared the qualitative variables among the two groups. A *t*-test or Mann–Whitney *U* test was used to compare quantitative variables according to their distribution.

We performed Poisson regression models to assess the association between the intervention and outcomes. The confounders were baseline clinical and demographic characteristics. Also, we performed a Kaplan–Meier curve to determine the differences in survival between the groups. A log-rank *p*-value of less than 0.05 is a statistically significant difference.

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Results

There was a total of 81 patients included in the study, with 41 in the high-dose arm and 40 in the low-dose group. The mean age was similar between groups (57.49 vs. 56.95 years). There were more male patients in the group of 24 mg (p = 0.01). Besides, patients on the 24 mg dose had more prevalence of hypertension (p = 0.052). Almost no patients received Remdesivir, Tocilizumab, or Interferon. Regarding laboratory exams, patients in the 24 mg group had a higher D-dimer median (405 vs. 100, p = 0.004). More patients in the 24 mg group had a higher rate of invasive mechanical ventilation (15.00% vs. 2.56%, p = 0.058) (Table 1).

When evaluating the association between the high-dose group and outcomes, we found no significant association with mortality, nosocomial infections, high-flow oxygen therapy, invasive mechanical ventilation, or the need for vasopressors (Table 2).

There were no significant differences in the Kaplan–Meier curve regarding survival (Log-rank p-val-

Table 1. Demographic and clinical characteristics of the included patients

Variable	24 mg group (n = 41)	8 mg group (n = 40)	p value
Age, mean (SD)	57.49 (2.57)	56.95 (2.37)	0.878[a]
Sex, n (%)			
Male	29 (70.73)	17 (42.50)	0.01[b]
Female	12 (29.27)	23 (57.50)	
Hypertension, n (%)	21 (51.22)	12 (30.00)	0.052[b]
Diabetes	7 (17.07)	8 (20.00)	0.735[b]
CKD	0 (0.00)	1 (2.50)	0.494[c]
HF	1 (2.44)	1 (2.50)	0.747[c]
Remdesivir use	0 (0.00)	1 (2.50)	0.494[c]
Tocilizumab use	1 (2.44)	0 (0.00)	0.506[c]
Interferon use	1 (2.44)	2 (5.00)	0.491[c]
Maximum RR, mean (SD)[d]	29.025 (6.99)	27.55 (5.12)	0.285[a]
Minimum neutrophil count, mean (SD)[d]	7,649.8 (516.00)	6,326.535 (644.25)	0.1129[a]
Minimum lymphocyte count, median (IQR)[d]	980 (700–1,200)	838.5 (499.5–1,325)	0.603[e]
Maximum CRP, median (IQR)[d]	46 (12–96)	24 (18–96)	0.617[e]
Maximun ESR, mean (SD)[d]	32.525 (2.53)	36.7 (2.56)	0.247[a]
Maximum LDH, median (IQR)[f]	406 (0–550)	405.5 (35–617)	0.368[e]
Maximum ferritin median (IQR)[f]	341 (0–609)	368 (42–867)	0.445[e]
Maximum D-dimer median (IQR)[f]	100 (0–282)	405 (100–717)	0.004[e]
Maximum procalcitonin median (IQR)[f]	0.25 (0–0.29)	0.25 (0.25–0.322)	0.238[e]
High flow mask[d], n (%)	14 (35.00)	7 (17.95)	0.086[b]
Invasive mechanical ventilation[d], n (%)	6 (15.00)	1 (2.56)	0.058[c]
Need of vasopressors[d]	1 (2.50)	1 (2.56)	0.747[c]
Nosocomial infection[f]	8 (21.62)	14 (40.00)	0.091[b]
Alive	35 (85.37)	38 (95.00)	0.140[c]

[a]Calculated using t-test.
[b]Calculated using Chi squared test.
[c]Calculated using Fisher's exact test.
[d]≤ 10% observations lost in one or both groups.
[e]Calculated using Mann Whitney U test.
[f]One group or both has > 10% of observations lost.
CKD: chronic kidney disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HF: heart failure; IQR: interquartile range; LDH: lactate dehydrogenase; RR: respiratory rate; SD: standard deviation.

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Table 2. Patient outcomes with different levels of organ support

Outcome	Crude model		Adjusted model[a]	
	RR	95% CI	RR	95% CI
Mortality	2.93	0.59–14.50	5.18	0.47–57.52
Nosocomial infections	0.87	0.58–1.30	0.85	0.55–1.33
High flow oxygen therapy	1.15	0.77–1.70	1.14	0.73–1.77
Mechanical ventilation	1.12	0.73–1.71	1.10	0.69–1.76
Need of vasopressors	0.99	0.65–1.55	0.99	0.61–1.62

[a]This model was adjusted by age, sex, hypertension, diabetes, chronic kidney disease, heart failure, remdesivir use, tocilizumab use, and interferon use.
CI: confidence interval; RR: relative risk.

ue = 0.315). However, from day 15, the 8 mg group seemed to have better survival (Fig. 1).

Discussion

We found no significant difference in mortality between the two strategies, but it seems that patients in the high-dose arm had higher D-dimers and required mechanical ventilation more often.

The optimal dose of dexamethasone remains controversial, especially for those who are escalating in oxygen requirements quickly. Although the RECOVERY trial has confirmed the usefulness of the drug in hypoxemic COVID-19 patients, the study was conducted in most European populations, which may not be adequately translated to Latin American countries.[1] The CoDEX study was conducted in a Latin American patient, similar to our study population, and was one of the first trials to utilize dexamethasone, although at a higher dose (i.e., 20 mg for five days then tapered to 10 mg for five days, after which it was stopped)[7] than the RECOVERY trial. This strategy was similar to the one utilized in the DEXA-ARDS study that found reduced ventilator-free days in patients treated with dexamethasone as opposed to the standard of care.[8] Higher D-dimers suggested a higher level of inflammation and lung injury, signifying that patients with higher levels were sicker than their low D-dimer counterparts.

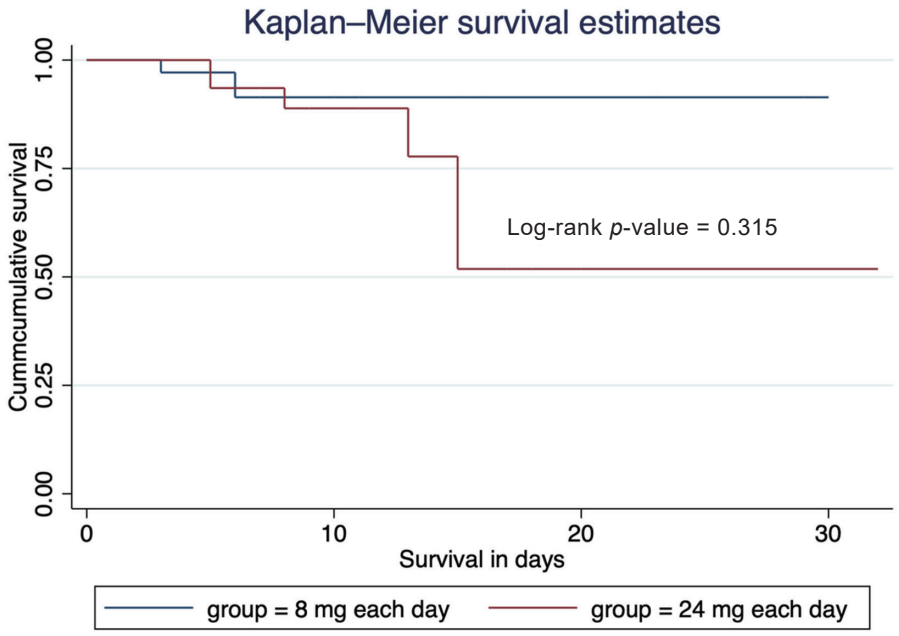

Fig. 1. Kaplan–Meier analysis of survival according to the dexamethasone group.
[The colored figure is used in the online version, available on the website http://doi.org/10.6705/j.jacme.202303_13(1).0005]

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Our paper is remarkable because it contrasts both strategies in a Latin American cohort and found no difference in outcomes in mortality. These findings are similar to other studies that have compared high and low-dose strategies for COVID-19, suggesting that an increased dose of dexamethasone does not impact patient outcomes in a significant manner. A trial comparing 6 mg vs. 12 mg of dexamethasone did not find the higher dose to impact outcomes,[6] and another trial that compared doses higher than 20 mg of dexamethasone (i.e., dexamethasone 40 mg/day and methylprednisolone 500 mg/day) found that the lower dose (< 6 mg/day) of dexamethasone improved outcomes.[9] Although it is unclear why higher doses do not improve mortality or ventilator-free days, this could be explained by possible adverse effects of therapy, such as the risk of opportunistic infections and hyperglycemia.

Although these results favor low-dose strategies, the optimal dose is still unclear since a recent Argentina study found that high-dose dexamethasone decreased ventilator days in a cohort of COVID-19 patients.[10] It could be argued that patient selection plays a role in who will benefit from lower to higher doses of steroids.

Our study has many limitations, such as being unblinded, single-center, and two different treatment teams (morning and afternoon shifts), which places a risk for selection and observer bias. Furthermore, the investigators did not fill the data collection sheet but rather by physicians taking care of the patients, which also lends itself to possible confounding bias. Finally, our paper had a small sample size that might not detect any difference. Most of our patients did not receive any other immunomodulating agent (IL-6i and JAK2i) that might impact outcomes in these patients. We believe that our paper is significant since it studies an underrepresented population in medical literature and helps delineate strategies for low-middle-income countries who might not be able to afford more expensive agents to dampen cytokine storms.

In conclusion, the higher dose of dexamethasone does not seem to decrease mortality in this single-center observational study, but further randomized trials are necessary to find a possible difference between strategies.

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