

The role of corticosteroids in patients hospitalized for COVID-19 at Mexico General Hospital

El papel de los corticoesteroides en pacientes hospitalizados por COVID-19 en el Hospital General de México

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Abstract

Objective: To compare the evolution of hospitalized patients infected with SARS-CoV-2 who received corticosteroid-based treatment versus patients who received standard therapy. **Method:** Retrospective, observational, and analytical study. Clinical records were collected from the different intensive care units, and data were obtained from confirmed Patients with COVID-19 over 18 years of age who were hospitalized. The population was divided into two groups: patients who received corticosteroid treatment, and those who received standard therapy. **Results:** A total of 1603 patients were admitted to hospital, and of these 984 (62.9%) were discharged due to death. The main result was the identification by odds ratio (OR: 4.68; 95% confidence interval [95%CI]: 3.75-5.83; $p = 0.001$) as risk for death to the use of systemic steroids, as well as the use of invasive mechanical ventilation (OR: 2.26; 95%CI: 1.80-2.82; $p < 0.001$). The male gender was the most affected with 1051 (65.6%) patients. Mean age was 56 years (± 14). **Conclusions:** Corticosteroid use was associated with poor prognosis in patients hospitalized for COVID-19 compared to those receiving standard therapy.

Keywords: COVID-19. Mortality. Corticosteroids. Acute respiratory failure.

Resumen

Objetivo: Comparar la evolución de los pacientes hospitalizados infectados por SARS-CoV-2 que recibieron tratamiento a base de corticoesteroides frente a los pacientes que recibieron la terapia estándar. **Método:** Estudio de tipo retrospectivo, observacional y analítico. Se recolectaron los expedientes clínicos de las diferentes unidades de terapia intensiva y se obtuvieron datos de los pacientes confirmados de COVID-19, mayores de 18 años, que estuvieron hospitalizados. Se dividió la población en dos grupos: pacientes que recibieron tratamiento con corticoesteroides y pacientes que recibieron terapia estándar. **Resultados:** De un total de 1603 pacientes ingresados a hospitalización, 984 (62.9%) fallecieron. El resultado principal fue la identificación mediante razón de momios (odds ratio [OR]: 4.68; intervalo de confianza del 95% [IC95%]: 3.75-5.83; $p = 0.001$) como riesgo para defunción con uso de esteroides sistémicos, así como con uso de ventilación mecánica invasiva (OR: 2.26; IC95%: 1.80-2.82; $p < 0.001$). El sexo masculino fue el más afectado, con 1051 (65.6%) pacientes. La media de edad fue de 56 años (± 14). **Conclusiones:** El uso de corticoesteroides se asoció con mal pronóstico en los pacientes hospitalizados por COVID-19, en comparación con los que recibieron la terapia estándar.

Palabras clave: COVID-19. Mortalidad. Corticoesteroides. Insuficiencia respiratoria aguda.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19 and emerged in Wuhan, China, in late 2019 from a zoonotic source. Most cases of COVID-19 are asymptomatic or result in mild illness^{1,2}. However, a substantial percentage of patients develop a respiratory illness that requires admission, and these infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support¹.

In critically ill patients with COVID-19, various drug such as remdesivir, hydroxychloroquine, lopinavir, and interferon had little or no impact on mortality, the need for intubation, or the length of stay³. Glucocorticoids (GC), including dexamethasone, have been widely used as effective anti-inflammatory and immunosuppressive drugs and may be beneficial to treat the SARS-CoV-2-induced cytokine storm. Several studies have discussed the application of GC to treat severe acute respiratory syndrome in 2002, Middle East respiratory syndrome in 2012, severe influenza, and community-acquired pneumonia^{1,4}.

The RECOVERY trial¹, a randomized clinical trial of over 6400 hospitalized patients with COVID-19, provided evidence for dexamethasone treatment at a dose of 6 mg once a day for up to 10 days. Dexamethasone reduced the 28-day mortality rate in those on ventilation support, with a 17% reduction in mortality. However, no benefit was found in patients who did not require oxygen. The clinical trials published have used intermediate to high doses, such as prednisone at 30 mg equivalent per day and dexamethasone at 125 mg.

Prior to this study, several guidelines on the management of COVID-19 either contraindicated or did not recommend the use of GC. Nevertheless, dexamethasone is on the World Health Organization list of essential drugs and is widely available worldwide at a low cost. Guidelines issued by medical authorities in the United Kingdom and the U.S. National Institutes of Health were updated to recommend the use of GC in hospitalized patients with COVID-19^{1,5}. As a result, dexamethasone is now considered the standard of care to treat patients with severe COVID-19⁶.

Several observational studies in Spain have shown a better response when GC is given in short cycles at high doses (equivalent to 300 mg to 600 mg of prednisone per day). The additional benefit of these doses may be due to the activation of the non-genomic

pathway of GC, resulting in maximum anti-inflammatory effects⁷.

In one study, Wang et al.⁸ found that the administration of methylprednisolone did not to reduce the risk of death in patients with COVID-19-related pneumonia. Twenty-three deaths were reported in 50 patients, which is a relatively high mortality rate (almost 50%). Therefore, in terms of indications, lower doses, and duration, the authors suggested that further research is needed regarding the use of methylprednisolone⁸.

Estimates have suggested that up to 12% of the patients hospitalized with COVID-19 have required invasive mechanical ventilation, and most have developed acute respiratory distress syndrome (ARDS). Histopathological examination of the lungs of patients with COVID-19 reveals diffuse alveolar damage with hyaline membranes, which is typical of ARDS. In addition, COVID-19 is often associated with an inflammatory state, which can contribute to multiple organ failure in patients. GC can have a significant impact on controlling this exacerbated response⁹.

The antiviral immune response is crucial for eliminating the invading virus. However, an inappropriate response can lead to systemic hyperinflammation and complications such as ARDS and multiple organ failure. Early treatment of this hyperinflammation may be important to reduce mortality in patients with COVID-19¹⁰.

Although most infected patients remain asymptomatic or develop mild symptoms, up to 20% may experience severe illness developing pneumonia and respiratory failure. Oxygen therapy is the cornerstone of support therapy and is required in nearly 15% of the cases, while invasive mechanical ventilation is necessary in 5% to 7% of severe cases. Given the high mortality rate in patients on invasive ventilation, halting the progression from moderate to severe respiratory failure should reduce COVID-19-related mortality¹¹.

The high concentration of inflammatory cytokines/chemokines amplifies tissue-destructive damage through endothelial dysfunction and vasodilation, thus allowing the recruitment of immune cells, including macrophages and neutrophils. Vascular leakage and compromised barrier function promote endothelitis and pulmonary edema, thus limiting gas exchange, and leading to hypoxemic respiratory and organ failure. The inflammatory environment induces endothelial cells to upregulate leukocyte adhesion molecules, thereby promoting the accumulation of immune cells, which can also contribute to the rapid progression of respiratory failure. Hyperinflammation in the lungs

also induces transcriptional changes in macrophages and neutrophils that perpetuate tissue damage, ultimately leading to irreversible lung damage. Recent evidence suggests that systemic inflammation can result in long-term sequelae in cardiac tissues^{12,13}.

GC are both anti-inflammatory and immunosuppressive; they bind to intracellular receptors to modulate the gene transcription of proinflammatory mediators. They also inhibit genes expressing the enzyme cyclooxygenase 2 to suppress the synthesis of prostaglandins, lipoxins, leukotrienes, and thromboxane. They have been used to treat a wide range of conditions, including various respiratory disorders such as bronchial asthma, chronic obstructive pulmonary disease, and pneumonitis¹⁴.

The objective of this study was to evaluate the use of GC in patients with COVID-19 hospitalized in various intensive care units (ICUs) of Hospital General de Mexico, Mexico City, Mexico. Records indicate the use of three GC (dexamethasone, hydrocortisone, and methylprednisolone), with no significant differences among these drugs at equivalent doses.

Method

This was a retrospective, observational, and analytical trial. The health records from patients with COVID-19 from the ICUs of Hospital General de Mexico were collected. As a protective measure, the records were disinfected using ozone sterilization.

Clinical data were obtained from patients older than 18 years who were hospitalized due to SARS-CoV-2 infection with a positive quantitative real-time polymerase chain reaction (qRT-PCR) test and who met the inclusion criteria from April 1 through December 31, 2020. All information was recorded in a database.

The study population was divided into 2 groups: patients who received systemic GC (dexamethasone, methylprednisolone, and hydrocortisone) and patients on standard therapy, to subsequently compare clinical outcomes. In the different ICUs, standard therapy included drugs such as anticoagulants, antibiotics, analgesics, and supplementary oxygen.

Descriptive statistics included frequency analysis (percentages) for categorical variables and means and standard deviations, or medians for the continuous ones. Comparisons were determined using the ANOVA test for continuous variables and the chi-square test for categorical ones. All *p* values were two-tailed, with a significance threshold of 0.05.

Results

A total of 1603 health records of adult patients hospitalized due to SARS-CoV-2 infection were included (Fig. 1), with a mean age of 56 years (± 14). Table 1 shows the main clinical variables of the study sample; and table 2 the values of the main biochemical variables.

In the 1603 health records on record, the mean length of stay was 12 days (± 11). The range of lengths of stay went from 0 to 109. We should mention that 141 hospitalized patients died within the first 48 hours of their stay, 68 of them within the first 24 hours. We should also mention that that, out of the 141 deaths reported within the first 48 hours, 109 (77%) did not receive a single dose of GC.

The main comorbidities in patients who received GC included hypertension (38.2%), diabetes mellitus (38.1%), and obesity (30.4%), while in patients on standard therapy, the main comorbidities were chronic kidney disease (52.5%), obesity (51%), and diabetes mellitus (49.3%).

In the health records of the 984 deceased patients, it was documented that 62.9% had received some systemic GC. A total of 365 (44.6%) out of the 819 patients who did not receive systemic GC, died compared to 619 (79%) who actually did (Fig. 2).

Regarding oxygen saturation, estimated by pulse oximetry, the mean was 73% (± 17). The fraction of inspired oxygen (FiO_2) administered to patients upon admission was, on average, 26% (± 15) (Fig. 3), indicating that while some patients did not require oxygen upon admission, others required immediate endotracheal intubation on mechanical ventilatory support at 100% FiO_2 .

When the health records of the 1603 hospitalized patients were split into 2 groups (those who received systemic GC and those who did not), a statistical analysis was performed using an independent samples *t*-test (results are shown in Table 3).

In the cross-tabulation analysis, an odds ratio (OR) of 4.68 was identified as a risk for death with the use of systemic GC (Table 4). Various models were created for binary logistic regression analysis (improvement/death), and potentially confounding variables were controlled for, while making sure that the introduction of new variables did not abruptly change the OR in the various models. Finally, the model with the greatest parsimony was obtained with the sole variable being the use of systemic GC, with an OR of 4.68 (95% confidence interval: 3.75, 5.83; *p* = 0.0001).

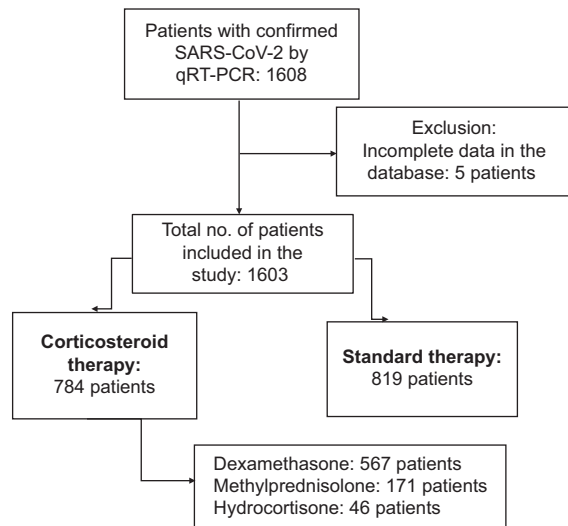


Figure 1. Flowchart depicting the number of patients included in each study group.

In other models, age and the values of d-dimer and C-reactive protein showed an OR slightly > 1, all with a p value of 0.0001.

Discussion

During the COVID-19 pandemic, the management of these patients was one of the main challenges for the entire health care personnel. This study reviewed the use of GC in patients with COVID-19 hospitalized in the ICUs of Hospital General of Mexico. Initially, empirical use of GC was one of the main treatments administered, showing benefits in many patients compared to other types of treatment. However, it would not be until the publication of the RECOVERY trial that it became clear that patients on invasive mechanical ventilation were the ones who benefited the most from GC, and that not all patients infected with SARS-CoV-2 were eligible for this management but rather had certain indications¹.

Various publications worldwide documented the scientific evidence of the benefits of GC in these types of patients¹⁵⁻¹⁷. However, there are also studies where a negative effect has been observed, especially in patients with comorbidities¹⁸⁻²⁰. For example, the study conducted by Provencio et al.²¹ stated that the risk of death was significantly higher in patients on GC during admission compared to those off GC (51.3% vs 25.7%; $p < 0.001$).

In Mexico, a significant portion of the population infected with SARS-CoV-2 had one or more of the

Table 1. Main clinical characteristics

	Frequency	Percentage* (n = 1603)
Sex		
Man	1051	66
Woman	552	34
Use of corticosteroids		
Not used	819	51
Dexamethasone	567	35
Methylprednisolone	171	11
Hydrocortisone	46	3
Use of antibacterial drugs		
Yes	1443	90
No	160	10
Use of anticoagulants		
Yes	498	31
No	1105	69
Mechanical ventilatory support		
Not required	1122	70
Required invasive mechanical ventilation	444	28
Other conditions	37	2
Reason for discharge		
Death	984	61
Improvement	619	39

*Rounded percentage.

Table 2. Blood values of biochemical parameters upon hospital admission (n = 1603)

Parameter	Mean $\pm$ SD	Range
D-dimer	4699 $\pm$ 9031	31-43.968
Leukocytes	11.319 $\pm$ 6.481	2.500-45.000
Neutrophils	9.753 $\pm$ 6.076	300-42.500
Lymphocytes	1.043 $\pm$ 1.837	100-35.800
Procalcitonin	2.6 $\pm$ 10.2	0.01-100
Ferritin	1.271 $\pm$ 1.550	2-9.966
High-sensitivity C-reactive protein	203 $\pm$ 128	1-479

SD, standard deviation.

main comorbidities, such as hypertension, diabetes mellitus, and obesity, among others²²⁻²⁴.

In our study of 1603 patients hospitalized due to SARS-CoV-2 infection, GC did not show therapeutic benefit. The analysis of GC use in ICUs showed higher mortality rates during admission and increased use of invasive mechanical ventilation. There was no significant difference in the length of hospitalization between patients on systemic corticosteroids and those on standard therapy. Men had higher rates of hospitalization

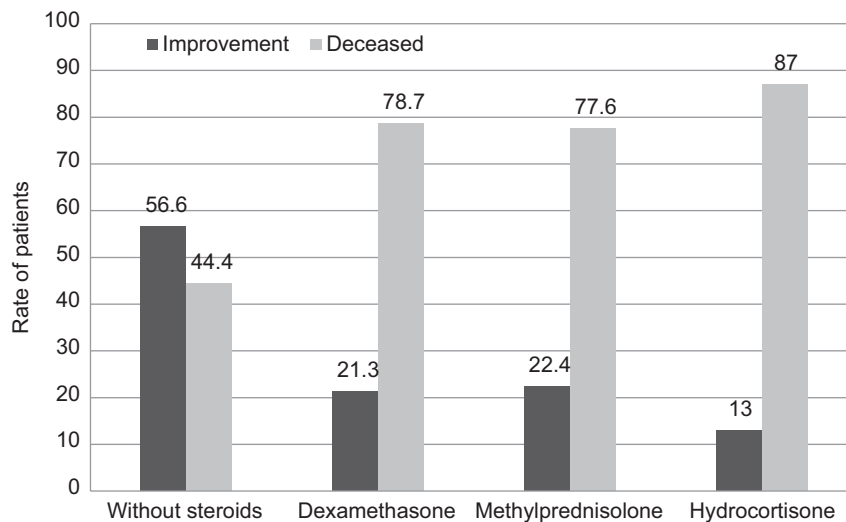


Figure 2. Reason for discharge and adjuvant therapies. Rate of discharges due to improvement with different treatments: no steroids ($n = 454$), dexamethasone ($n = 121$), methylprednisolone ($n = 38$), and hydrocortisone ($n = 6$). Rate of discharges due to death with no steroids ($n = 363$), with dexamethasone ($n = 446$), with methylprednisolone ($n = 132$), and with hydrocortisone ($n = 40$).

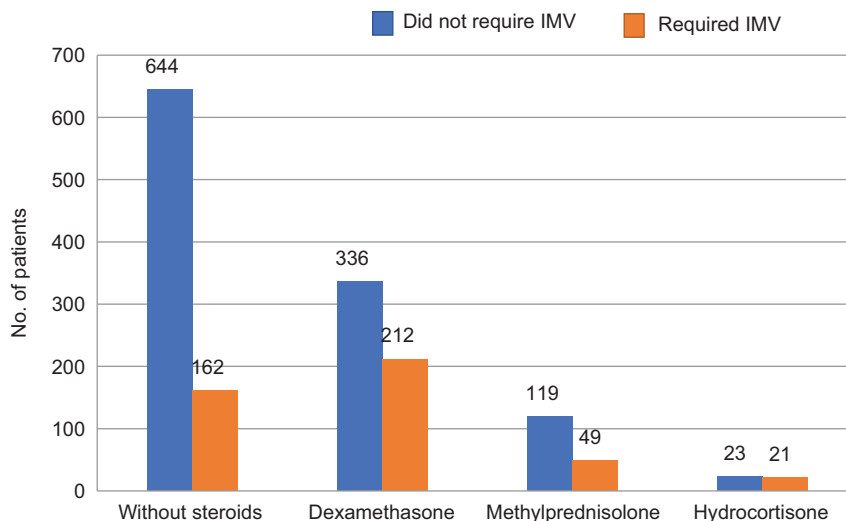


Figure 3. Use of invasive mechanical ventilation (IMV) and adjuvant therapies.

and more requirements for GC. Among the different GC used, methylprednisolone was associated with lower mortality rates and less use of invasive mechanical ventilation. In contrast, hydrocortisone was associated with a poorer prognosis, requiring more mechanical ventilation. Patients on standard therapy (anticoagulants, antibiotics, and supplementary oxygen) had more discharges due to improvement and a lower use of invasive mechanical ventilation.

One of the major limitations of this study is that not all variables used for stratifying the severity of the

disease from a clinical perspective were identified in the health records. This requires us to interpret the results presented with caution since the use of systemic GC was likely due to the greater severity of the disease, along with the clinical deterioration of patients who ultimately died, and it was not the cause or associated with the patients' deaths. Interpreting it otherwise would lead to accepting a "spurious association" or "reverse causality."

Another possible bias in the statistical analysis performed was the lack of information due to incomplete

Table 3. Comparison between groups of patients on any type of systemic corticosteroid and those who did not it (n = 1603)

	Group on corticosteroids	Group off corticosteroids	p (95%CI)
Age, years	53.6	58.1	0.0001 (−6.73 to −2.32)
Hospitalization days	10.9	13.1	0.010 (−3.89 to −0.54)
Pulse oximetry (%)	76.2	71.0	0.0001 (2.58 to −7.81)
D-dimer (ng/mL)	3350	5937	0.0001 (−4023 to −1149)
Blood leukocytes (cells/mm ³)	10 112	12 444	0.0001 (−3.30 to −1.36)
Blood neutrophils (cells/mm ³)	8538	10 884	0.0001 (−3.25 to −1.43)
High-sensitivity C-reactive protein (mg/L)	188	216	0.031 (−51.99 to −2.53)

95%CI: 95% confidence interval.

Table 4. Association between the use of corticosteroids and hospitalization outcomes

Corticosteroid Therapy	OR (95% CI)	p
Mortality (n = 619)	4.68 (3.75 to −5.83)	< 0.001
Use of invasive mechanical ventilation (n = 282)	2.26 (1.8 to −2.82)	< 0.001

CI: confidence interval; OR: odds ratio.

health records. For example, not all records included the dosages and duration of GC treatment. Additionally, not all the variables that had something to do with the reason for discharge, such as inflammatory markers, were analyzed, and it was also unknown whether there were patients who self-medicated with GC at home.

Inhaled GC could be a therapeutic intervention for patients with COVID-19, since they have proven to reduce inflammatory marker levels in ARDS, and also appear to improve pulmonary physiology^{14,25}. We believe that to improve the administration of different GC (dexamethasone, methylprednisolone, or hydrocortisone) in patients with COVID-19, it is necessary to analyze the presence of comorbidity with each of them and thus have better clinical management of this disease.

Conclusions

In hospitalized patients with COVID-19, the use of different GC (dexamethasone, methylprednisolone, or hydrocortisone) was associated with a poor prognosis. Patients on GC during admission had higher mortality rates and required more invasive mechanical ventilation compared to those on standard therapy alone.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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