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Revista Clínica Española 221 (2021) 592–595

Revista Clínica Española

www.elsevier.es/rce

BRIEF ORIGINAL

Caution with the use of dexamethasone in patients with COVID-19 in its initial phases*

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Received 20 February 2021; accepted 22 February 2021
Available online 17 September 2021

KEYWORDS
COVID-19;
Dexamethasone;
Cytokine storm

Abstract
Introduction: The effect of dexamethasone in the initial phase of infection by SARS-CoV-2 and its influence on COVID-19 is not well defined. We describe clinical-radiological characteristics, the cytokine storm parameters, and the clinical evolution of a series of patients treated with dexamethasone in the disease's initial phase.
Method: A study of 8 patients who received dexamethasone before the development of COVID-19. We evaluate clinical variables, imaging tests, cytokine release parameters, treatment used and patient evolution.
Results: All patients received a 6 mg/day dose with a mean duration of 4.5 days before admission. High resolution computed tomography (HRCT) revealed that most of them presented a severe extension; most patients had a slightly elevated level of cytokine release parameters. Three patients required high-flow oxygen therapy due to respiratory failure; none required orotracheal intubation or died.
Conclusion: Dexamethasone in the early stages of SARS-CoV-2 infection appears to be associated with severe COVID-19.

* Please cite this article as: Callejas Rubio JL, Aomar Millan I, Moreno-Higueras M, Martín Ripoll L, Yuste Osorio E, Ríos-Fernández R. Precaución con el uso de dexametasona en pacientes con COVID-19 en sus fases iniciales. Rev Clín Esp. 2021;221:592–595.
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PALABRAS CLAVE
COVID-19;
Dexametasona;
Síndrome de tormenta de citoquinas

Precaución con el uso de dexametasona en pacientes con COVID-19 en sus fases iniciales

Resumen
Introducción: El efecto de la dexametasona en la fase inicial de la infección por SARS-CoV-2 y su influencia sobre la COVID-19 no está bien definido. Describimos las características clínico-radiológicas, los parámetros de tormenta de citoquinas y la evolución clínica de una serie de pacientes tratados con dexametasona en la fase inicial de la enfermedad.
Método: Estudio de 8 pacientes que recibieron dexametasona previo al desarrollo de la COVID-19. Evaluamos variables clínicas, pruebas de imagen, parámetros de liberación de citoquinas, el tratamiento empleado y su evolución.
Resultados: Todos los pacientes recibieron una dosis de 6 mg/día con una duración media de 4,5 días previos al ingreso. La mayoría de los pacientes presentaron una extensión grave en la tomografía computarizada de alta resolución (TCAR) y una elevación leve de los parámetros de liberación de citoquinas; tres pacientes requirieron oxigenoterpia nasal de alto flujo (ONAF) por insuficiencia respiratoria, y ningún paciente requirió intubación orotraqueal ni falleció.
Conclusión: La dexametasona en las fases iniciales de la infección por SARS-CoV-2 parece asociarse con una COVID-19 grave.

Introduction

COVID-19 is a two-phase disease with an initial viremic phase and a later immune-response phase. During the latter, a minority of patients may develop severe disease, characterized by a hyperinflammatory response defined as cytokine storm syndrome, which can cause respiratory failure and death.

Dexamethasone has been demonstrated to reduce mortality in a group of patients who presented with severe pneumonia.[1] The role of dexamethasone in the initial phase of COVID-19 and its influence on the second phase are not well-established; indeed, its use may even be detrimental, causing an increase in the viral load.[2,3]

We reviewed the cases of eight patients hospitalized for COVID-19 in our hospital who had received outpatient treatment with dexamethasone. We described their clinical, analytical, and radiological characteristics as well as their progress during the hospitalization.

Objectives

This work aims to describe the clinical and radiological characteristics, inflammatory response, and clinical progress of a series of patients hospitalized due to SARS-CoV-2 pneumonia who had received treatment with dexamethasone prior to their admission.

Patients and methods

We reviewed the medical records of all patients admitted to our hospital due to SARS-CoV-2 pneumonia in the period from January 1 to January 31, 2021. Patients whose medical histories indicated the use of dexamethasone prior to admission because of infection were selected. Clinical, radiological, and analytical data were gathered as well as data on progress of the patients who had received treatment at the time of admission.

We used a semiquantitative system developed by the British Thoracic Imaging Society[4] in order to classify lung involvement as mild (<25%), moderate (25%–50%), or severe (≥51%).

We reviewed the medical records of all patients who died due to COVID-19 in our hospital during this period and determined if dexamethasone use prior to their admission was indicated in their medical history.

Results

A total of eight patients had received outpatient treatment with dexamethasone. Their demographic, radiological, and analytical characteristics as well as the treatment used and their progress are shown in Table 1.

There were five women and three men with a mean age of 50.2 years (33–73). All patients received a dexamethasone dose of 6 mg/day, with a mean of 4.5 days of treatment (3–6) prior to admission. The PaO_2/FiO_2 ratio was greater than 300 mmHg in all eight patients. In the six cases in which high-resolution computed tomography (HRCT) imaging was available, five (83.3%) had severe involvement. Just two of the eight patients (25%) had ferritin levels greater than 500 μg/dL and none had levels greater than 1000 μg/dL.

In regard to treatment used, pulses of 6-methylprednisolone at a dose of 2 mg/kg/day for three to five days were used in all cases. One patient also received treatment with anakinra. High-flow nasal oxygen (HFNO) was necessary in three (37.5%) patients due to onset of

Table 1 Characteristics of patients who received dexamethasone.

	1	2	3	4	5	6	7	8
Age	57	33	56	56	73	70	57	56
Sex	Female	Men	Female	Men	Female	Female	Men	Female
Dexamethasone dose (mg/day)	6	6	6	6	6	6	6	6
Days of treatment before admission	5	3	6	4	4	5	4	5
PaO_2/FiO_2 (mmHg)	305	310	310	324	305	310	305	310
HRCT Involvement	Severe	Severe	Moderate	Not performed	Severe	Not performed	Severe	Severe
Ferritin (μg/L)	378	181	335	579	385	413	133	881
D-dimer (mg/L)	0,29	0.41	1.6	0.25	0.56	0.33	0.7	0.6
CRP (mg/dL)	205	21	35	63	25	25	133	72
Treatment	6MP pulses HFNO	6MP pulses	6MP pulses	6MP pulses Anakinra	Dexamethasone HFNO	6MP pulses HFNO	6MP pulses	6MP pulses

HNFO: high-flow nasal oxygen; CRP: C-reactive protein; HRCT: high resolution computed tomography; 6MP: 6-methylprednisolone.

respiratory failure during the hospitalization. None required intubation and there were no deaths.

None of the patients who died due to COVID-19 in our hospital during the study period had received outpatient treatment with dexamethasone.

Discussion and conclusions

Patients with prior dexamethasone treatment who were admitted to our hospital due to SARS-CoV-2 pneumonia presented with extensive infiltrates on the HRCT imaging test and more than one-third of them required HFNO during the hospitalization. Nevertheless, the final outcome was favorable in all cases, with no need for orotracheal intubation and no fatal outcomes.

Following publication of the RECOVERY study,[1] which demonstrated that treatment with dexamethasone decreased mortality in patients with severe COVID-19 pneumonia, it is no surprise that many of us physicians have felt tempted to administer it in some patients who fall outside of the clinical trial's inclusion criteria. However, its role in these situations is not known.

Based on the results of studies conducted in patients with systemic autoimmune diseases, it is known that corticosteroid use at mean doses of 10 mg/day or higher of prednisone or equivalent is linked to a significant increase in mortality.[5,6] This is mainly correlated with an increase in viremia or a decrease in viral clearance.[7] In our small series, although there were no deaths, the extension of the pneumonia observed on the HRCT imaging tests was severe and several patients required HFNO.

However, this is in contrast to the inflammatory response markers, which were significantly lower than what is expected with this disease. When we compared the C-reactive protein (CRP) and ferritin levels of patients treated as outpatients with the mean of our series of patients with cytokine storm syndrome treated at the beginning of the pandemic with pulse corticosteroid therapy,[7] we observed significantly lower levels of ferritin (410.5 vs. 1031 μg/L) and CRP (72.3 vs. 105.2 mg/dL). It is possible that dexamethasone may somehow halt cytokine storm markers,[8] though the complex pathophysiological mechanism through which respiratory failure occurs does not stop with early use of the drug.[9,10]

The limitations of this study are its small sample size, a lack of data on cytokine release markers at the time dexamethasone was initiated, and the fact that we do not know the progress of all patients who received outpatient treatment with this drug and did not come in to the hospital.

Until study results demonstrate a beneficial effect of early use of corticosteroids in the initial SARS-CoV-2 viremia phase, we believe that they should not be habitually used except in patients who require them due to other diseases.

Funding

No funding has been received for this study.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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