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Pre-hospital treatment of COVID-19 patients from a reference hospital in Mexico City

Tratamiento prehospitalario en COVID-19 atendidos en un hospital de referencia de la Ciudad de México

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ABSTRACT. Introduction and objective: more than a year after the emergence of COVID-19, many drug therapies have been considered, all based on a critical evaluation of the emerging literature. The main objective of our study was to know the pre-hospitalary treatment of patients with COVID-19. **Material and methods:** we reviewed 101 clinical records of hospitalized patients at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas National (INER) diagnosed with COVID-19 during the second wave of the pandemic. A database was created, and descriptive statistics were performed using the software GraphPad Prism version 8. **Results:** the mean age of the patients was 52.3 (± 11.9) years. Patients received 4-5 medications as pre-hospital treatment; the most commonly prescribed medications were corticosteroids and antibiotics. **Conclusions:** COVID-19 patients received a large number of unnecessary medications during pre-hospital medical care; several of them were prescribed despite the lack of scientific evidence on their use and the national and international recommendations for treating the disease.

Keywords: COVID-19, SARS-CoV-2, pre-hospitalary treatment.

RESUMEN. Introducción y objetivo: a más de un año del surgimiento de la COVID-19, se han considerado muchas terapias farmacológicas, todas basadas en la evaluación crítica de la literatura emergente. El objetivo principal de nuestro estudio fue conocer el tratamiento prehospitalario de los pacientes con COVID-19. **Material y métodos:** se revisaron 101 expedientes clínicos de pacientes hospitalizados en el Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER) con diagnóstico de COVID-19 durante la segunda ola de la pandemia. Se conformó una base de datos y se realizó estadística descriptiva utilizando el programa GraphPad Prism versión 8. **Resultados:** el promedio de edad de los pacientes fue de 52.3 (± 11.9) años. Los pacientes recibieron de 4-5 medicamentos como tratamiento prehospitalario; los medicamentos que más se prescribieron fueron corticosteroides y antibióticos. **Conclusiones:** los pacientes con COVID-19 recibieron un gran número de medicamentos innecesarios durante la atención médica prehospitalaria; varios de ellos se prescribieron a pesar de la falta de evidencia científica sobre su uso y de las recomendaciones nacionales e internacionales para tratamiento de la enfermedad.

Palabras clave: COVID-19, SARS-CoV-2, tratamiento prehospitalario.

INTRODUCTION

SARS-CoV-2 disease (COVID-19) described in December 2019 resulted in a pandemic with a rapidly increasing incidence. More than two years after the emergence of COVID-19, many pharmacologic therapies have been considered for its treatment and it has been necessary to frequently update practices on their use based on a critical evaluation of the emerging literature. Practices related to the evaluation and treatment of COVID-19 during the first six months of the pandemic varied widely around the world. Depending on the severity of illness, supportive measures were adjusted: patients with mild disease usually recovered at home, with minimal care and isolation, while patients with moderate disease had to be monitored frequently, and sometimes hospitalized,[1] because they could progress to critical illness with hypoxemic respiratory failure and require prolonged ventilatory support.[2]

Initially, there was interest in the repositioning of drugs such as chloroquine and hydroxychloroquine,

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sometimes accompanied by azithromycin, based on reports of randomized clinical trials with a small sample size.[3,4] Both drugs have been used in the treatment of autoimmune diseases due to their immunomodulatory effects and particularly for their action on proinflammatory cytokines, including interleukin-1 (IL-1) and IL-6.[5] Their use in COVID-19 was justified by the antiviral effects that these drugs exert in vitro against SARS-CoV-2 and, in association with azithromycin, it was suggested that they could reduce viral load.[3,4] In Mexico, on June 6, 2020, the «Recommendations for the treatment of infection by SARS-CoV-2, causative agent of COVID-19» were published, proposing the use of these drugs.[6] With the passage of time and the publication of international studies, it was observed that there was no beneficial effect of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19.[7,8] The RECOVERY (Randomized Evaluation of COVID-19 Therapy) clinical trial showed that hydroxychloroquine did not decrease mortality in hospitalized patients compared to standard treatment (supportive care).[9] On December 23, 2020, the Infectious Diseases Society of America (IDSA) amended its guidelines to dismiss the use of hydroxychloroquine plus azithromycin as a strong recommendation, with evidence of moderate certainty.[10]

Glucocorticoids were also initially suggested due to concerns about the presence of a hyperinflammatory state that causes the severe manifestations of COVID-19, and other immunomodulatory therapies were also investigated. Several therapeutic interventions were proposed to mitigate the inflammatory organ injury in this viral pneumonia and the value of glucocorticoids was widely discussed.[11] A trial involving the use of a short course of methylprednisolone showed beneficial effect only in patients over 60 years of age with severe COVID-19; however, uncertainty remained about the use of glucocorticoids.[12] Later, the RECOVERY trial reported that dexamethasone reduced mortality among hospitalized patients with COVID-19, although the benefit was limited to patients receiving supplemental oxygen, being greatest among patients requiring mechanical ventilation.[13] In its September 2020 update, the IDSA added dexamethasone as a recommendation with moderate certainty evidence;[10] however, this drug did not improve the prognosis of patients who did not receive supplemental oxygen and could have undesirable effects; therefore, it is not recommended for the treatment of mild or moderate COVID-19.[1]

The use of ivermectin was evaluated empirically in uncontrolled studies for COVID-19,[14] and subsequently its use was not recommended outside the context of a clinical trial.[10] On March 31, 2021 the World Health Organization issued a warning on the inappropriate use of ivermectin for the treatment of COVID-19, considering the lack of scientific evidence about its efficacy and safety in the treatment of this disease.[15]

Antimicrobials have been overused during the COVID-19 pandemic. Some, such as doxycycline, because of the assumption that their intracellular effects could reduce viral replication, as well as prevent cell damage and expression of inflammatory molecules.[16] Others, such as macrolides, because of their potential immunomodulatory effect[17] that could counteract the exaggerated inflammatory process of COVID-19, have been used singly and in combination with other drugs.[4] Currently, antibiotics are only recommended when there is clinical and/or microbiological evidence of bacterial infection associated with SARS-CoV-2 pneumonia and short treatment regimens should be considered.[1]

Considering the clinical guidelines on the use of various drugs against COVID-19, the aim of this study was to describe the drugs that were indicated on an outpatient basis (prior to hospitalization) to patients seen at INER during the second upsurge of cases.

MATERIAL AND METHODS

The clinical records of 101 patients hospitalized at the *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* (INER) with a diagnosis of COVID-19 were reviewed, during the period from April to September 2021, when there was a spike in cases, according to information from the General Directorate of Epidemiology of Mexico. All patients who were admitted to INER, who signed the informed consent (patients or their relatives) and who had the complete file for review were included. Convenience sampling was performed.

Patient demographic data, pathologic history, days of evolution and symptoms of the disease and the outcome at hospital discharge were collected; a database was formed and descriptive statistics were performed using GraphPad Prism, version 8. The treatments that patients received on an outpatient basis (before hospitalization) were analyzed to determine whether there was an association with death or discharge due to patient improvement. Medications were separated by drug group and subsequently the Mann-Whitney U test (nonparametric) was performed to determine if there were differences between groups; a $p \leq 0.05$ was considered significant. The frequency of indication was also described, which refers to the number of times a drug was indicated, as some patients were prescribed the same drug on several different occasions during their evolution.

This project followed the ethical considerations mentioned in the declaration of Helsinki,[18] as last updated in Fortaleza, Brazil, and is part of protocol E08-20,

approved by the INER Ethics and Research Committee. The confidentiality of the patients' personal data was maintained.

RESULTS

Table 1 summarizes the demographic characteristics of the study population. Of the 101 patients studied, the mean age was 52.3 years (± 11.9); 55% of the patients were discharged due to improvement, while 39% died. Most patients had a history of obesity (50.5%), followed by systemic arterial hypertension (36.6%) and diabetes mellitus (26.7%). The average number of days spent in hospital was 10.9 days. Among the symptoms mainly reported by the patients or their relatives were fever (60.4%), myalgia (45.5%) and headache (40.6%). The respiratory symptom most frequently reported by patients or their relatives was dyspnea (83.2%); gastrointestinal symptoms were the least frequently reported, including diarrhea (9.9%), abdominal pain (3.0%) and vomiting (2.0%). On admission, patients had a mean oxygen saturation of 63% (± 18.4).

Table 2 shows the different drugs used for outpatient treatment of SARS-CoV-2 infection grouped according to the function of each type of drug, e.g., antibiotics, nonsteroidal anti-inflammatory drugs, etcetera. Some drugs were grouped under the name «airways», despite having different mechanisms of action, considering that their usefulness lies in improving the patient's ventilatory process. The table also shows the number of times each drug was prescribed and the number of patients in whom it was prescribed.

The patients received between four and five medications as prehospital treatment. The most frequently prescribed medications were corticosteroids and antibiotics. Dexamethasone was the most prescribed corticosteroid (47 patients); while, in the antibiotic group, azithromycin was found in first place (31 patients), followed by ceftriaxone (25 patients), levofloxacin (15 patients) and clarithromycin (11 patients).

Nonsteroidal anti-inflammatory drugs (NSAIDs) were the third most frequently prescribed group of drugs on an outpatient basis for the treatment of COVID-19; a total of 41 persons were prescribed paracetamol, while 20 were given ibuprofen. Antihistamines and anticoagulants were prescribed in a smaller proportion; enoxaparin was the anticoagulant with the highest frequency of indication (nine patients). The patients or their relatives also reported the prescription of bronchodilators, and four patients were also prescribed immunomodulators.

Table 1: Demographic characteristics of the population studied, N = 101.

	n (%)
Demographic characteristics	
Age*	52.3 ± 11.9
Body mass index (kg/m^2)	31.6 ± 6.1
Deaths	40 (39.6)
Discharges due to improvement	55 (54.5)
Transfer/voluntary discharges	1 (1.0)
Pathological history	
Obesity‡	51 (50.5)
Systemic arterial hypertension	37 (36.6)
Diabetes *mellitus*	27 (26.7)
Alcoholism	7 (6.9)
Pulmonary disease§	16 (15.8)
Heart disease¶	4 (4.0)
Kidney disease	2 (2.0)
Liver disease	1 (1.0)
Days of evolution*	10.9 ± 5
Symptoms	
Fever	61 (60.4)
Headache	41 (40.6)
Myalgias	46 (45.5)
Arthralgias	42 (41.6)
General condition attack	75 (74.3)
Dyspnea	83 (83.2)
Cough	52 (52.5)
Rhinorrhea	11 (10.9)
Odynophagia	31 (30.7)
Diarrhea	10 (9.9)
Abdominal pain	3 (3.0)
Hyporexia	16 (15.8)
Vomiting	2 (2.0)
Dysosmia	11 (10.9)
Oxygen saturation on admission*	63% (± 18.4)

* Mean ± standard deviation.
‡ Obesity was defined as body mass index > 30, according to the criteria established by the World Health Organization.
§ Four patients had chronic cough, four had chronic obstructive pulmonary disease, two had nonspecific interstitial pneumonia, two had interstitial disease, one had pulmonary fibrosis and one had asthma.
¶ All four patients had chronic heart failure.

DISCUSSION

The COVID-19 pandemic has generated difficulties in patient care, initially due to the lack of knowledge of the virus and the disease itself, as well as the sudden increase of cases in all countries, which sometimes exceeded the capacities of the different health systems in the world. Over time, treatment guidelines emerged based on recommendations from the countries that handled the first cases of this disease. Initially, these recommendations included drugs used in various viral infections and anti-inflammatory drugs in general, and later key points observed in severe patients, such as systemic inflammation and coagulation alterations, were considered.

Table 2: Medications indicated in the study population for outpatient management of SARS-CoV-2 infection, N = 101.

Drug	Frequency of indication	Number of patients, (%)
Antibiotics		
Azithromycin	31	31 (30.7)
Ceftriaxone	25	25 (24.7)
Levofloxacin	15	15 (14.9)
Clarithromycin	11	11 (10.9)
Amikacin, amoxicillin	4	7 (6.9)
Cefixime, cephalexin, moxifloxacin, penicillin, cefotaxime	2	10 (9.9)
Erythromycin, lincomycin, ciprofloxacin, nitrofurantoin, benzylpenicillin, ampicillin, ertapenem, clindamycin, norfloxacin, cefuroxime, cephalothin	1	8 (7.9)
NSAIDS		
Paracetamol	41	41 (40.6)
Ibuprofen	20	20 (19.8)
Aspirin	12	12 (11.9)
Metamizole	10	10 (9.9)
Naproxen	3	3 (2.9)
Meloxicam	2	2 (1.9)
Nimesulide, lysine clonixinate, serratiopeptidase, diclofenac	1	4 (3.9)
Airways		
Ambroxol	12	12 (11.9)
Acetylcysteine	5	5 (4.9)
Ipratropium bromide + salbutamol	4	4 (3.9)
Salbutamol	6	6 (5.9)
Doxofylline, bromhexine, dextromethorphan, levodropropizine, theophylline, benzonatate	1	6 (5.9)
Corticosteroids		
Dexamethasone	47	47 (46.5)
Prednisone	14	14 (13.8)
Budesonide/formoterol, budesonide/ipratropium bromide	4	8 (7.9)
Beclomethasone, betamethasone	3	7 (6.9)
Methylprednisolone	2	2 (1.9)
Deflazacort/salmeterol/fluticasone propionate, dexamethasone + ipratropium bromide/ salbutamol, fluticasone	1	3 (2.9)
Antihistamines		
Loratadine	3	3 (2.9)
Chlorphenamine	2	2 (1.9)
Anticoagulants		
Enoxaparin	9	9 (8.9)
Rivaroxaban	4	4 (3.9)
Apixaban	4	4 (3.9)
Heparin	3	3 (2.9)
Dabigatran	1	1 (0.9)
Clopidogrel	1	1 (0.9)
Antivirals		
Oseltamivir	18	18 (17.8)
Lopinavir/ritonavir	2	2 (1.9)
Amantadine, acyclovir, elvitegravir/cobicistat/emtricitabine/tenofovir	1	3 (2.9)
Immunomodulators		
Interferon beta, gamma globulin, pidotimod, tocilizumab	1	4 (3.9)

NSAIDs = non-steroidal anti-inflammatory drugs.

By the beginning of the second wave of the COVID-19 pandemic, sufficient information was already available regarding the effectiveness of some of the repositioning drugs for emergency use in the treatment of patients with COVID-19. Based on clinical studies, clinical practice guidelines were modified, ruling out the effectiveness of the use of chloroquine or hydroxychloroquine, the combination of hydroxychloroquine with azithromycin, and ivermectin.[10] Although the use of dexamethasone was found to reduce mortality in hospitalized patients with COVID-19, its usefulness was restricted only for patients requiring supplemental oxygen and/or mechanical ventilation.[13]

In this review, we evaluated the follow-up of recommendations in guidelines for the treatment of COVID-19, with a focus on prehospital primary care, and assessed whether there was a correlation with the outcome of patients seen at INER. It was observed that despite existing recommendations for the treatment of patients with COVID-19, dexamethasone and prednisone were prescribed in half of the patients during the primary care they received prior to admission to INER. Prescription of antibiotics without evidence of bacterial infection was also observed, with azithromycin being the most commonly used.

No differences in outcome were observed in patients who were prescribed steroids prior to hospitalization compared to those who were not. These results are consistent with Annane's review, where glucocorticoid use was not associated with an increased risk of bacterial infection or delayed viral clearance.[19]

An interesting fact we found in this study is that all types of medications were applied in patients who initially had a mild symptom picture and apparently did not prevent patients from developing a severe picture requiring hospitalization, considering that all of them were admitted to INER for medical care. However, one of the limitations of the study is the difficulty of analyzing the effect of prehospital treatment on hospital treatment and the outcome of the patients, considering that we found a large number of variables related to the amount and type of drugs used, as well as the variables of the individuals themselves, such as age, sex and presence of comorbidities, which together may contribute to the evolution of the disease.

CONCLUSIONS

Given the lack of a specific treatment against SARS-CoV-2 virus, and the variety of clinical manifestations, including the severity of the clinical picture, it is important to follow the recommendations of national and international health authorities, which are based on the most recently generated scientific evidence, and which consider different population groups for their development. The use of repositioning drugs has been a commonly used option in clinical practice. However, the lack of knowledge of the pathophysiology of the disease and the inability to predict the outcome of each patient should not be a reason to abuse unnecessary drugs, such as antibiotics, which involves other important problems in global public health, such as bacterial resistance. It is not advisable to exceed the use of other drugs that have proven useful in a specific group of patients, such as steroids, since their indiscriminate use could have unfavorable consequences on clinical outcome. Furthermore, the adverse effects of all drugs should be considered, especially when they are used in combination; their use should be prudent in patients with a disease that is still being studied worldwide.

REFERENCES

1. Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. N Engl J Med. 2020;383(18):1757-1766. doi: 10.1056/nejmcp2009249.
2. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3.
3. Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. Cell Discov. 2020;6(16):6-9. doi: 10.1038/s41421-020-0156-0.
4. Gautret P, Lagier JC, Parola P, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.
5. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol. 2012;42(2):145-153. doi: 10.1007/s12016-010-8243-x.
6. Secretaría de Salud. Recomendaciones para el tratamiento de la infección por SARS-CoV-2, agente causal de COVID-19. Coronavirus.gob.mx. Published online 2020:1-8.
7. Cavalcanti AB, Zampieri FG, Rosa RG, *et al*. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020;383(21):2041-2052. doi: 10.1056/nejmoa2019014.
8. Rosenberg ES, Dufort EM, Udo T, *et al*. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA - J Am Med Assoc. 2020;323(24):2493-2502. doi: 10.1001/jama.2020.8630.
9. The RECOBERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020;383(21):2030-2040. doi: 10.1056/NEJMoa2022926.
10. Bhimraj A, Morgan RL, Shumaker AH, *et al*. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis. 2020: ciaa478.
11. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020;395(10225):683-684. doi: 10.1016/S0140-6736(20)30361-5.
12. Corral-Gudino L, Bahamonde A, Arnaiz-revillas F, Gómez-Barquero J. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. Published online 2020:1-24. doi: 10.1101/2020.06.17.20133579

13. The RECOBERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704. doi: 10.1056/nejmoa2021436.
14. Babalola OE, Bode CO, Ajayi AA AF. Ivermectin shows clinical benefits in mild to moderate COVID19: a randomised controlled double blind dose response study in Lagos. Published online 2021. doi: doi.org/10.1101/2021.01.05.21249131.
15. World Health Organization. La OMS desaconseja usar ivermectina para tratar la COVID-19 si no es en ensayos clínicos. Tratamiento de la COVID-19 con ivermectina.
16. Sagris M, Kokkinidis DG, Lempesis IG, *et al*. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev Cardiovasc Med. 2020;21(4):565-575. doi: 10.31083/J.RCM.2020.04.264.
17. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. Int J Antimicrob Agents. 2020;56(2):106053. doi: 10.1016/j.ijantimicag.2020.106053.
18. Association WM. World medical association declaration of Helsinki ethical principles for medical research involving human subjects. JAMA - J Am Med Assoc. Published online 2013:2013-2016. Available in: https://jamanetwork.com/journals/jama/fullarticle/1760318
19. Annane D. Corticosteroids for COVID-19. J Intensive Med. 2021;1(1):14-25. doi: 10.1016/j.jointm.2021.01.002.

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