STUDY OFFICIAL TITLE (original title is in Spanish. This is a translation into English)

Ivermectin, Corticoids, Aspirin and Enoxaparin in the treatment of COVID-19

REGISTRY NUMBER (CLINICALTRIALS.GOV)

NCT04425863

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IDEA

HYPOTHESIS

The use of Ivermectin, aspirin, enoxaparin and dexamethasone in different doses and combinations may reduce the effects of COVID 19, the need of ICU treatment and the mortality rate.

STUDY PROTOCOL (SUMMARY)

Site	Dr. Alberto Eurnekian Hospital, Ezeiza, Province of Buenos Aires, Argentina
Study type	Single-centre, prospective
Justification	COVID-19 emergency requires the urgent development of strategies to avoid the impact of the disease on our population, the saturation of the health system and that allows us to carry out adequate treatments to reduce the mortality of the disease. Severe forms of the disease strongly suggest two pathophysiological states: Hypercoagulability and Hyperinflammation. We propose the use of Ivermectin associated with Aspirin, Dexamethasone and Enoxaparin, in patients affected by COVID-19
Working hypothesis	The early association identified between SARS-CoV with SARS-CoV-2 was confirmed later by tests on protein S (spike) that characterizes these two viruses, which prove that S proteins from both viruses are extremely similar. The only significantly different portion is a furin-binding domain in the SARS-CoV-2 protein S, which has been speculated to make possible the expansion of tropism or the increase of virus transmission, compared to SARS-CoV from 2003. On the other hand, one of the most conserved portions of the protein is the receptor-binding domain (RBD), which has a similar (or reportedly higher) affinity to angiotensin converting enzyme type 2 (ACE2) in comparison with SARS CoV. This functional receptor is found in tissues, including lung alveolar epithelium, arterial and venous endothelium, smooth muscle, renal tubular epithelium, and small intestine epithelium, largely explaining the clinical presentation of COVID-19 patients.

	However, the involvement of organs with a much lower concentration of these receptors (eg: CNS), shows that there is -at least- other form (s) of deleterious action. The incubation period for the virus has been calculated at 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% of patients are said to have symptoms at 11 days (95% CI 8.2 to 15.6 days). A mortality of 5.7% has been calculated. The average COVID patient presents with fever (78%), cough (60-79%), and myalgia or fatigue (35.8-44%). 55% develop dyspnea, which appears on average 8 days after the onset of symptoms. To the manifestations expressed above, we must add the presence –almost sine qua non- of bilateral conjunctival injection, without associated secretions, hypogeusia, skin rash and hyposmia. However, in times of pandemic, any of these signs or symptoms, even in isolation, should put the patient under suspicion of contagion. Diagnostic confirmation is carried out through laboratory studies, which can be performed on a wide variety of biological specimens, Bronchoalveolar lavage samples showed the highest sensitivity (93%), followed by sputum (72%), nasal swabs (63%), fiberoptic bronchoscope brush biopsy (46%), pharyngeal swabs (32%), feces (29%) and, finally, blood (1%). A sensitivity of 91% is reported in saliva samples. Computed Axial Tomography (CT) is very useful as a complementary study in the diagnostic approach of COVID-19, since it has found a sensitivity of 97% (95% CI 95-98%) and a negative predictive value of 80% (95% CI 76 to 89%) when compared to RT-PCR (Reverse Transcriptase Polymerase Chain Reaction). Nevertheless, this does not discredit the monitoring by conventional radiology, if more sophisticated means are not available. Coronaviruses are positive single-stranded RNA viruses, members of the Coronaviridae family, part of the order Nidoviridae. There are four genera (alpha, beta, delta and gamma coronaviruses), of which the first two are responsible for respiratory diseases in humans and gastrointestinal diseases in animals.

	Species pathogenic for humans include SARS-CoV, MERS-CoV, HCoVNL63 and HCoV-229E, HCoV-OC3 and HCoV-HKU, and the recently discovered SARS-CoV-2. En los últimos 20 años, se han registrado 3 grandes brotes de coronavirus a nivel mundial. In the last 20 years, there have been 3 major outbreaks of coronavirus worldwide. Evidence suggests that a subset of patients with severe forms of COVID 19 may have a syndrome known as a cytokine storm. The current treatment of COVID-19 is supportive ("compassionate use"), and respiratory failure due to acute respiratory distress syndrome (ARDS) is the leading cause of mortality. Secondary hemophagocytic lymphohistiocytosis (SHLH) is a poorly recognized hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia with multiple organ failure. In adults, SHLH is most often triggered by viral infections, occurring in 3.7–4.3% of sepsis cases. The cardinal features of sHLH include constant fever, cytopenias, and hyperferritinemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients. A cytokine profile that resembles sHLH is associated with the severity of COVID-19 disease, characterized by an increase in interleukin (IL) -2, IL-7, granulocyte colony stimulating factor, protein 10 inducible by interferon-γ, monocyte chemoattractant protein, macrophage inflammatory protein 1 -α, and tumor necrosis factor-α. Mortality predictors from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng / ml in non-survivors vs 614.0 ng / ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$), suggesting that mortality could be due to viral hyperinflammation. However, cases have been reported in which tissue and organ involvement was found whose concentration of ECA2 receptors is very dissimilar (myocardium, brain). In all of them, the common denominator was small vessel thrombosis, as observed in entities such as Catastrophic Antiphospholidic Syndrome (SAC). HYPERCOAGULABILITY: More than a century ago, Virchow proposed that thrombus formation and spread was caused by abnormalities in three key areas: • Blood flow • The vascular wall • Blood components These three factors are known as Virchow's triad. At present the factors of the Virchow triad have been limited in greater detail: Circulatory stasis: abnormalities of hemorheology and turbulence in vascular bifurcations and stenotic regions.

	Injury to the vascular wall: abnormalities in the endothelium, such as atherosclerosis and associated vascular inflammation. Hypercoagulable state: abnormalities in the coagulation and fibrinolytic pathways and in platelet function associated with an increased risk of VTE and other cardiovascular diseases (such as coronary artery disease [CPA], heart failure and stroke in patients with AF). All lead to a state of hypercoagulability, which could explain the formation of microthrombosis in different locations.
Outcomes	1. Number of patients improving or not worsening their condition after 7 days of treatment 2. Number of patients needing ICU treatment after 14 days 3. Number of deaths 30 days after enrollment 4. Number of patients having serious adverse events after 30 days.
Population	Patients complying with acceptance criteria and willing to sign informed consent at Eurnekian Hospital in a period from May to July
Eligibility criteria	**Inclusion criteria** 1. Adults of any sex and children with the consent of tutors or parents. 2. Positive for COVID-19 3. Capable of understanding and sign the informed consent in written form. **Exclusion criteria** 4. Hypersensitivity or allergy to any of the drugs used 5. Children under 5 years old 6. Pregnant women **Discontinuation criteria** 7. Subjects using any other compassionate medication during study 8. Serious adverse event that may place the subject at risk according to the investigator's judgement

Treatments

CASE	Ivermectin	Dexamethasone	Anticoagulant	O_2/Ventilation
Mild	24 mg (oral solution 5 mg/mL) on days 0 and 7	None	Aspirin 1 250-mg Tablet daily for 30 days	None
Moderate	36 mg (oral solution 5 mg/mL) on days 0 and 7	1 daily 4-mg injection until discharge	Enoxaparina 1 mg /Kg de peso (100 UI/Kg.) dos veces al día	Low – flow washed oxygen or oxygen concentrator
Severe	48 mg (oral solution 5 mg/mL) on days 0 and 7	1 daily 4-mg injection until discharge	Enoxaparin 100 IU / kg (ca. 1 mg/kg) daily until discharge	Mechanical ventilation

Study design

All patients testing positive for COVID-19 from June 1st to July 1st who complied with inclusion criteria and willingly signed the informed consent were classified as mild, moderate, or severe cases according to the following criteria:

Mild stage	Moderate stage	Severe stage
Only mild symptoms and no clinical sign of viral pneumonia	3 severe symptoms or 2 severe and 2 mild symptoms. Clinical signs of viral pneumonia	4 severe symptoms or 3 severe symptoms and not less than 2 mild symptoms. Clinical signs of bilateral viral pneumonia

Symptoms were classified as mild or severe according to the following table:

MILD SYMPTOMS	SEVERE SYMPTOMS
Fever not above 38.5 °C	Fever above 38.5 °C
Isolated diarrheal episodes	Diarrhea (more than 3 daily depositions)
Hyposmia or Hypogeusia	Flictenular conjunctivitis
Mild desaturation (93 – 96 %)	Strong desaturation (92% or less)
Dyspnea without matter	Tachypnea (FR> 25 / minute)
Polymyoarthralgias, Persistent headache, Abdominal pain	

Statistical analysis	Percentage of each of the variables measured during the study in each group will be presented. Overall mortality rate and mortality rate of hospitalized patients (i.e moderate and severe cases together) will be compared with literature values as follows: - Overall mortality will be compared via chi squared with the mortality rate in Argentina. Risk and Number Needed to Treat variables will be calculated. - Mortality rate of hospitalized patients will be compared with mortality rate of inpatients treated otherwise within the same hospital where the study was conducted and with literature data. Risk and Number Needed to Treat variables will be calculated.