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Heparin and Tocilizumab in Patients with Severe COVID-19: The HEPMAB Randomized Clinical Trial

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Abstract

Clinical presentation of severe Coronavirus disease 2019 (COVID-19) is associated to an intense inflammatory response and thrombogenesis. The benefits of the association of interleukin-6 receptor blockade (tocilizumab) and therapeutic-dose anticoagulation remains unclear. We aimed to assess whether heparin and tocilizumab could effectively reduce inflammation and thrombogenesis in severe COVID-19 patients.

This is an open-label, multicenter, randomized, clinical trial, involving patients with severe COVID-19 infection. Eligible patients were randomly assigned in a 1:1:1:1 ratio to receive either therapeutic or prophylactic anticoagulation with heparin, with or without an intravenous single dose of tocilizumab. The participants in the study were assigned to one of the four distinct arms: 1) therapeutic anticoagulation; 2) prophylactic anticoagulation; 3) therapeutic anticoagulation plus a single intravenous dose of tocilizumab; and 4) prophylactic anticoagulation plus a single intravenous dose of tocilizumab. The primary outcome was clinical improvement at day 30, defined as a composite of hospital discharge and/or a reduction of at least 2 points of the modified ordinal scale of 7 points recommended by the World Health Organization.

Thus, the investigators hypothesized that the use of heparin and tocilizumab could potencially reduce inflammation and thrombogenesis in patients with severe COVID-19 infection, improving patients outcomes and survival.

Troubleshooting

Safety warnings

RISKS AND BENNEFITS

The mortality of patients with severe pneumonia caused by COVID-19 is around 40 to 60% in ICUs worldwide. So far, there is no specific treatment proven to be effective for this disease. Pathophysiology studies of the pulmonary form and systemic form of COVID-19 show inflammation and thrombogenesis in this disease. Therefore, the assessment of the use of heparin and tocilizumab is necessary based on this rationale. Heparin is a medication widely used in critically ill patients, safe and validated in several clinical trials. The main side effect is bleeding, however, respecting its contraindications, as discussed in the exclusion criteria, the risk is minimal. Tocilizumab is an already used and approved medication in patients with rheumatoid arthritis and in patients with cytokine release syndrome associated with CART-Cells infusion. It is a safe medication, the main care being the monitoring of infectious worsening due to immunosuppression. Our patients will be monitored according to strict intensive care protocols.

ADVERSE EVENTS

An adverse event (AE) is any undesirable medical occurrence in a clinical trial participant with a drug and is not necessarily causally related to the treatment.
Bleeding is the most common adverse effect of heparin and heparin-induced thrombocytopenia (HIT) is a known adverse event of the use of UFH with an incidence between 0.5 to 5%.27 Clinical and laboratory evidence should be used to evaluate the presence of HIT, by reason that HIT antibodies may not be available for several days.
The most reported adverse reactions related to the use of tocilizumab are: (I) severe infection: including pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis; (II) gastrointestinal tract perforations: as a complication of diverticulitis, including acute peritonitis, lower gastrointestinal perforation, fistula, and abscess; (III) reaction during infusion: the most frequently reported event during infusion was hypertension and within the first 24 hours, headache and skin reactions; (IV) anaphylaxis: reaction observed during the infusion of the second to fourth administration of tocilizumab; and (V) altered laboratory parameters: such as thrombocytopenia, elevation of liver enzymes and lipid profile (total cholesterol, LDL, triglycerides).28
Serious adverse events (SAE) that:
a) result in death or potentially fatal;
b) need hospitalization or prolonged hospitalization;
c) result in persistent or significant disability or incapacity;
d) significant medical occurrences – at the discretion of the researcher responsible for the project and/or assistant physician.
The occurrence of SAE will be notified if the event is:
a) related: an event that results from the administration of any research procedure;
b) unexpected: event that is not listed in the protocol as an expected occurrence.

The protocol's Serious Adverse Events must be reported to the Local Ethics Committee within 24 hours of knowledge by the researcher/study team responsible for the participating site.
Given the severity of the disease in COVID-19, there is no study pre-specifying follow-up interruption criteria. The protocol team will review blinded AE/EAG data every 2 weeks. If there are a worrying number of unexpected AEs, the researcher will request a review of the safety data in an ad hoc meeting with the independent external safety monitoring committee, which should take place in real time, by videoconference. In addition, all serious adverse events identified during the study will be analyzed by the CEP (Committees of Ethic in Researches)/CONEP (National Council of Ethics in Research) system.

Ethics statement

Ethical considerations

The protocol will be conducted in accordance with the terms of the guidelines and regulatory standards for research involving human beings - Resolutions No. 466/12, 346/05, 441/2011 and complementary Resolutions of the National Health Council / National Comission of Ethics in Researches (CONEP).
Due to the seriousness of the disease, in some situations considering a situation of substantial decrease in the participant's decision-making capacity, the informed consent may initially be directed to their legal guardian, who will be invited to participate in the research protocol after the verbal presentation, reading the consent form, time for reflection and questions and will sign the consent form. After the research participant recovers the decision-making capacity, the consent form will be reapplied.
The coordinating center will submit the protocol to the CEP/CONEP system and approval of the protocol, consent form and related documents will be obtained prior to the start of the study. According to the II Report to the CEP, on April 14, 2020, of the CONEP and due to the exceptional nature adopted for research protocols related to COVID-19, the CEP of the participating centers will endorse the approved opinion, when applicable, issued by CONEP.
It is the responsibility of the principal investigator to ensure that all conditions for study approval are met and that protocol changes or serious adverse events are also reported to the Ethics Committee.
The trial was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Ministry of Science and Technology, Brazil. The agency did not have any role in the study conception, data analysis or writing of the report.

Before start

Rationale for drug doses

The doses of heparin used in the study are doses already internationally recommended in the classic indications of the medication. UFH and LMWH are safe and widely indicated in critically ill patients. Heparin is a medication routinely used to prevent and treat venous thromboembolism.
Tocilizumab is an immunomodulatory medication that, at a dose of 8 mg/kg per dose, has been shown to be safe in patients treated with rheumatoid arthritis and cytokine release syndrome.

HEPMAB Study Protocol

1 INTRODUCTION

Coronavirus 2019 related Severe Acute Respiratory Syndrome (COVID-19) quickly evolved from an epidemic outbreak in Wuhan, China, to a pandemic affecting more than 2 million individuals worldwide. Although COVID-19 infection primarily manifests as a respiratory tract infection, new evidence indicates that this disease presents systemic involvement, including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems. 1-4.

Recent studies have shown that, in its pathophysiology, inflammation and thrombogenesis predominate, especially in severe forms of COVID-19. The activation of cytokines such as IL-1, IL-6, and interferon-gamma results in pulmonary infiltration in a systemic inflammatory syndrome and in coagulation activation, which can culminate in organ failure and death.5

Studies have shown an increase in the frequency of findings of thromboembolism in these patients, with deep vein thrombosis (DVT) occurring around 25%, which may also be related to a worse prognosis.6

In a retrospective multicenter study during the first two months of the epidemic in China, 260 of 560 patients (46.4%) with a confirmed diagnosis of COVID-19 infection had elevated D-dimer (≥0.5 mg/L), while the elevation was more pronounced in severe cases (59.6% versus 43.2% in non-serious patients).7 Other studies and a meta-analysis including four studies demonstrated that, despite methodological limitations, elevated D-dimer levels, and the presence of disseminated intravascular coagulation (DIC) are common findings in patients with the most severe forms of COVID-19 infection.8 The increase in D-dimer levels also seems to be a marker of the presence of coagulopathy, and its increase on admission and its gradual increase during clinical evolution is associated with a worse prognosis.9-11

Autopsy studies support the hypothesis of the presence of a state of hypercoagulability and inflammation in these critically ill patients, demonstrating that the high incidence of microthrombi may suggest a direction for complex therapeutic decisions in severe infections caused by COVID-19.12

Thus, the presence of clinical and laboratory parameters whose phenotypic profile expresses inflammation and thrombogenesis such as increased D-dimer, ferritin, C-reactive protein, and interleukin-6 in patients with severe infections by COVID-19 identify a population at higher risk and who could benefit from anticoagulant and anti-inflammatory therapy to prevent complications.

So far, only retrospective studies have been described suggesting a benefit of anticoagulation with heparin and immunomodulatory therapy with tocilizumab in improving the survival of these patients.

2 Primary objective:

To assess the efficacy of heparin and tocilizumab in patients with severe COVID-19.

3 Secondary objectives:

Assess whether the use of heparin and tocilizumab results in clinical improvement of patients within 30 days after randomization, defined by hospital discharge or a reduction of at least 2 points from baseline according to the World Health Organization's ordinal scale.

Evaluate the effect of heparin and tocilizumab on the following parameters in 30 days:
- Length of stay in the intensive care unit (ICU);
- Length of hospital stay;
- Need for endotracheal intubation;
- Duration of mechanical ventilation;
- Radiological changes;
- Time of radiological and tomography pattern improvement;
- Time of use of vasopressors;
- Sequential Organ Failure Assessment (SOFA) Score;
- Need for renal replacement therapy;
- Incidence of cardiotoxicity;
- Incidence and severity of acute respiratory distress syndrome;
- Secondary infection.
- Incidence of adverse events (AEs);
- Incidence of grade 3 and 4 serious adverse events (SAEs);
- Proportion of discontinuation or temporary suspension of treatment (for any reason);
- Improvement of laboratory parameters within 30 days or at hospital discharge: arterial blood gas, PaO2/FiO2 ratio, white blood cell count, hemoglobin, platelets, creatinine, urea, glucose, total bilirubin and fractions, aspartate transferase (AST), alanine transferase (ALT), prothrombin time, thromboplastin time, creatine kinase-MB (CK-MB), creatine phosphokinase (CPK), lactic dehydrogenase, C-reactive protein (CRP), interleukin 6 (IL-6), D-dimer, troponin, N-terminal fragment of brain natriuretic peptide (NT-pro-BNP), and ferritin;
- Incidence of venous thromboembolism (VTE) and bleeding for 30 days;
- Mortality in 30 days, 60 days, and 90 days.

4 HYPOTHESIS

The combination of therapeutic anticoagulation and the use of tocilizumab is superior to the other treatments in the clinical improvement of patients with severe COVID-19.

5 Trial design:

Randomized, open-label, 2×2 factorial-design (4 groups), clinical trial with concealed allocation 1:1:1:1 (central randomization; group 1. therapeutic anticoagulation; group 2. prophylactic anticoagulation; group 3. therapeutic anticoagulation with tocilizumab; group 4. prophylactic anticoagulation with tocilizumab) and intention-to-treat analysis.

6 Study population:

Adult patients, confirmed cases of COVID-19, will be included consecutively. Patients who have met the inclusion and exclusion criteria and who have signed the consent form will be submitted to randomization.

7 Inclusion criteria:

- Age ≥ 18 years;
- Informed consent form signed by the patient or guardian or by audio with the guardian;
- Positive result for COVID-19 in PCR (polymerase chain reaction) in nasopharyngeal swab and/or radiological evidence of COVID-19, by chest radiography or chest computed tomography (moderate, severe, or critical pneumonia; WHO ordinal scale ≥ 4);
- Need for ≥ 4 L of supplemental oxygen to maintain peripheral oxygen saturation equal to or greater than 93% or need for invasive mechanical ventilation.

8 Exclusion criteria:

Risk of bleeding:
- Clinical: active bleeding, major surgery in the last 30 days, gastrointestinal bleeding within 30 days;
- Laboratory: platelet count <50,000, INR> 2 or APTT> 50s;
- Known or suspected adverse reaction to unfractionated heparin (UFH), including heparin-induced thrombocytopenia (HIT);
- Adverse reaction or allergy to tocilizumab;
- Use of any of the following treatments: UFH to treat a thrombotic event within 12 hours before inclusion; low molecular weight heparin (LMWH) in therapeutic dose within 12 hours before inclusion; warfarin (if used 7 days before and if international normalised ratio (INR) greater than 2); thrombolytic therapy within 3 days before; and use of glycoprotein IIb / IIIa inhibitors within the previous 7 days;
- Pregnant or lactating;
- Absolute indication of anticoagulation due to atrial fibrillation or diagnosed thromboembolic event;
- Refusal by family members and/or patient;
- Active tuberculosis;
- Bacterial infection confirmed by culture;
- Neutropenia (<1000 neutrophils/mm3);
- Use of another immunosuppressive therapy that is not a corticosteroid;
- Septic shock.

9 Randomization and allocation concealment:

- Patients who have met the inclusion and exclusion criteria and who have signed the consent form will be submitted to randomization.
- The randomization process will consist of a central computer-generated random list in permuted blocks with variable sizes of 2, 4 and 6, and stratified by center. Central randomization will be at a 1:1:1:1 ratio into 4 groups. The allocation of patients will be done in a veiled way to patients and researchers who will analyze the outcomes.

10 Trial interventions:

Group 1 - Therapeutic anticoagulation

(I) Intravenous UFH started at a dose of 18 IU/kg/h, adjusted according to a nomogram to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times the reference value; or
(II) Subcutaneous LMWH - enoxaparin 1 mg/kg per dose every 12 hours.

Group 2 - Prophylactic anticoagulation

(I) Subcutaneous UFH 5,000 IU every 8 hours; or
(II) Subcutaneous LMWH - enoxaparin 40 mg daily.

Group 3 - Therapeutic anticoagulation with tocilizumab

(I) Intravenous UFH initiated at a dose of 18 IU/kg/h, adjusted according to a nomogram to achieve an aPTT of 1.5 to 2.0 times the reference value associated with 8 mg/kg/tocilizumab infusion / intravenous dose in a single dose; OR
(II) Subcutaneous LMWH - enoxaparin 1 mg/kg per dose every 12 hours associated with an infusion of tocilizumab 8 mg/kg/dose in a single dose.

Group 4 - Prophylactic anticoagulation with tocilizumab

(I) Subcutaneous UFH 5,000 IU every 8 hours associated with an infusion of tocilizumab 8 mg/kg/intravenous dose in a single dose; or
(II) Subcutaneous LMWH - enoxaparin 40 mg daily associated with an infusion of tocilizumab 8 mg/kg/intravenous dose in a single dose.

11 Recommendations for the use of heparin:

The choice of the type of heparin should be based on two criteria – creatinine clearance and hemodynamic stability. In the presence of reduced creatinine clearance (< 40 mL/min/m2) or shock (use of norepinephrine for hemodynamic control), give preference

to the use of intravenous heparin. Anticoagulation will continue until discharge from the ICU, or until death, or whichever comes first. Age > 75 years – correct enoxaparin to 0.75 mg/kg/12h dose.

12 Instructions for using tocilizumab:

The single dose of tocilizumab (for participants randomized to groups 3 and 4) should be administered exclusively intravenously, according to the patient's body weight, as shown in the table below:

	Body weight	Dosage
	45 to 65.9 kg	400 mg
	66 to 85.9 kg	600 mg
	Above 86 kg to 100.9 kg	800 mg

The standard dilution for each ampoule of Tocilizumab 200mg/10mL must be in 100 mL of 0.9% saline solution and the drug infusion must be carried out within 60 minutes.

13 DATA COLLECTION

Data will be registered in an electronic form. Demographic data, information on the presence of comorbidities, clinical signs and symptoms, laboratory results, and imaging tests on admission will be recorded. All laboratory and radiographic examinations, including chest radiography and computed tomography of the chest, will be performed at the attending physician's discretion and following the center's care routine.
The following records will be obtained up to the 30th day, discharge from the ICU or death: multiorgan dysfunction index by the Sequential Organ Failure Assessment score (SOFA)13, the results of laboratory tests including arterial blood gases, PaO2/FiO2 ratio, leukocyte count, hemoglobin, platelets, creatinine, urea, glucose, total bilirubin and fractions, AST, ALT, prothrombin time, activated partial thromboplastin time, CM-MB, CPK, lactic dehydrogenase.
Specifically for the protocol, the dosage of IL-6, D-dimer, troponin, C-reactive protein, NT-pro-BNP, and ferritin will be performed immediately after randomization, in 72 hours (D3) and 7 days after the start of treatment (D7). Blood samples will be collected by the centers participating in the study and sent to the Central Laboratory of the Instituto do Coração (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP).
12-lead electrocardiogram, lower limb Doppler ultrasound, and transthoracic

echocardiogram may be performed immediately after randomization, on the 7th and 30th day of ICU stay, or until hospital discharge.
The treatment administered will also be recorded: corticosteroids, chloroquine/hydroxychloroquine, antibiotic therapy, and ventilatory support (high-flow nasal catheter, non-invasive ventilation, mechanical ventilation).
In the presence of mechanical ventilation, the ventilatory mode, tidal volume, positive end-expiratory pressure (PEEP), plateau pressure and mean airway pressure, partial oxygen pressure (PaO2) / inspired oxygen fraction (FiO2) ratio will be recorded.

Table 1. Visiting and assessment schedule

	Mandatory (M) Opitional (O)	Visiting item	D1	D3	D7	D30 * (± 3 days)	D60* (± 10 days)	D90* (± 15 days)
	M	Eligibility review	X					
	M	Informed consent	X					
	M	Randomization	X					
	M	Demographics and medical background (including comorbidities, co-infections and previous medications)	X					
	M	Administration of Tocilizumab or not (according to the group allocated)	X					
	M	Administration of Heparin (the form will depend on the allocated group and clearance of creatinine)	X	X	X	X		
	M	Other medications	X	X	X	X	X	X
	M	Physical examination and vital signs	X	X	X	X		
	M	Clinical severity score	X	X	X	X		

	M	Respiratory parameters	X	X	X	X	X	X
	M	Blood sample collection for evaluation inflammatory profile	X	X	X			
	M	Assessment of adverse events (serious and non-serious)	X	X	X			
	O	Radiographic evaluation	X	X	X	X		
	O	12-lead ECG, transthoracic echocardiogram and lower limb Doppler ultrasound	X		X	X		
	O	Blood sample collection for hematology and biochemistry (blood count, creatinine, urea, AST, ALT, PT, aPPT, total bilirubin and fractions, CK-MB, CPK, LD, PCR)	X	X	X	X		

ECG, electrocardiogram; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TP, prothrombin time; aPTT, activated partial thromboplastin time; CK-MB, creatine phosphokinase MB fraction; CPK, creatine phosphokinase; LD, lactic dehydrogenase; CRP, C-reactive protein; IL-6, interleukin 6; NT-pro-BNP, N-terminal fragment of brain natriuretic peptide. *D30 and D90 visits can be made via telephone contact if the participant has been discharged from the hospital.

14 OUTCOMES

7.1. Primary outcome

The proportion of patients with clinical improvement at day 30, defined by hospital discharge or a reduction of at least 2 points compared to baseline on the 7-point WHO ordinal scale, as follow:

Seven-point ordinal scale:

1. Not hospitalized, with no limitations on activities;
2. Not hospitalized, but limited to activities;
3. Hospitalized, with no need for supplemental oxygen;
4. Hospitalized, needing supplemental oxygen;
5. Hospitalized, requiring high flow oxygen therapy, non-invasive mechanical ventilation or both;
6. Hospitalized, requiring ECMO, invasive mechanical ventilation or both;
7. Death.

This scale has been shown to be appropriate to identify the effect of an intervention on COVID-19 previously.14,15

15 Key secondary outcome:

All-cause mortality on day 30.

16 Secondary outcomes

- Length of stay in the ICU;
- Length of hospital stay;
- Rate of invasive mechanical ventilation;
- Time of invasive mechanical ventilation;
- Time for radiographic and tomographic pattern improvement;
- Time of use of vasopressors;
- SOFA score on the 3rd and 7th day of the ICU;
- 30-day dialysis fee;
- Renal failure by AKIN criteria within 30 days;
- Incidence of cardiotoxicity within 30 days;
- Incidence and severity of acute respiratory distress syndrome (ARDS);
- 30-day venous thromboembolism rate;
- Bleeding in 30 days;
- Secondary infection within 30 days;
- Mortality in 30, 60, and 90 days.

17 Safety outcomes:

Major bleeding:
- Fatal bleeding;
- Decrease in the hemoglobin level of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red cells;
Heparin-induced thrombocytopenia (HIT);
Serious adverse events associated with tocilizumab.

18

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