Managing Endothelial Dysfunction in COVID-19: A Randomized Clinical Trial at the Lebanese American University Medical Center- Rizk Hospital

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Main Information

Primary registry identifying number
LBCTR2021014651

Protocol number
000000

MOH registration number
000000

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
28/10/2020

Primary sponsor
LAUMCRH

Primary sponsor: Country of origin
Lebanon

Date of registration in primary registry
08/02/2021

Date of registration in national regulatory agency
28/10/2020

Public title
Managing Endothelial Dysfunction in COVID-19: A Randomized Clinical Trial at the Lebanese American University Medical Center-Rizk Hospital

Acronym
MEDIC-LAUMCRH

Scientific title
Managing Endothelial Dysfunction in COVID-19: A Randomized Clinical Trial at the Lebanese American University Medical Center-Rizk Hospital

Acronym
MEDIC-LAUMCRH

Brief summary of the study: English

Endothelial dysfunction has been proven to be one of the major mechanisms by which COVID-19 is causing illness to the human body. We aim to study the effectiveness and tolerability of a medication protocol aimed at improving endothelial dysfunction in COVID-19 infected patients.
The Protocol contains a statin (atorvastatin) a beta blocker (nebivolol) combined with L-arginine, nicorandil and folic acid.

The endothelium in summary is monolayer lining the arteries, veins and microvasculature. The endothelium hence plays a major role in homeostasis with interactive roles in blood pressure regulation, anti-coagulation and immune protection Moreover, it is thus relevant to note that the most common comorbidities that present with COVID-19 such as hypertension, diabetes, obesity and old age are all underlined by pre-existing endothelial damage or dysfunction. As such, endothelial dysfunction and oxidative stress and their relation to the manifestation and progression of COVID-19 infections has gain significant traction in recent publications. This breakthrough exposes several causes of endothelial dysfunction which include direct lining attack, hypoxia, cytokine storm and suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide deficiency. Several studies have emphasized the role of NO signaling as a major regulator of vascular tone and its antioxidant, anti-inflammatory and antithrombotic activity. For example, augmenting the production of NO and its bioavailability by nicorandil has been proposed as a potential treatment in patients with COVID 19. Nicorandil (a vasodilatory agent composed of N-[2-hydroxyethyl] -nicotinamide nitrate) used among patients with acute heart failure emergencies However, it has never been tested in patients with cardiovascular complications resulting from COVID 19 . Statins are cardioprotective in nature with recent reports showing that they can be beneficial in COVID-19 . An important mechanism via which Statins may improve endothelial function include increasing the production of NO and subsequent vasodilation effect, along with its established major anti-inflammatory and anti-oxidant properties . Nebivolol, a cardio-selective beta blocker has also shown non-adrenergic vasodilating properties via the release of NO along with antioxidative and anti-atherosclerotic activities. Furthermore, eNOS overexpression leads to an increase in NO formation only when the BH4 synthase GTP-cyclohydrolase 1 (GCH-1) is alsoup-regulated. So, Folic Acid and L-arginine will be given to supplement our patients with BH4 . We hypothesize that its administration along with the other previously mentioned agents would improve endothelial function in patients suffering from COVID 19 via a cumulative increase in the bioavailability of Nitric Oxide (NO), and thus improving patients' outcomes by demonstrating a clinical improvement as measured by the six-category ordinal scale. The secondary endpoints will include improvement in laboratory parameters, assessment for need of invasive mechanical ventilation, length of ICU stay, length of hospital stay, length of need for mechanical ventilation, all-cause mortality, and occurrence of side effects.

This hypothesis was formulated based several studies which expressed that endothelial dysfunction and oxidative stress are one of the major pathophysiological mechanism at the root of multiple causes of mortality and morbidity in COVID-19 patients. However, currently no randomized clinical trial evaluating this concept exists. Therefore, to provide the scientific evidence for the endothelial dysfunction protocol as part of the treatment regimen for SARS-CoV -2 infection, a trial is warranted.

Brief summary of the study: Arabic

من خلال COVID-19 تهدف هذه الدراسة الى تقييم قدرة وفعالية العلاج في تحسين الخلل البطاني للأوعية الدموية عند المرضى المصابين بـ
تقييم أولي للتحسن السريري حسب المؤشرات والمقياس الترتيبي ذي الفئات الست. ستشمل نقاط التقييم الثانوية: الحاجة إلى التنفس الاصطناعي،
طول مدة الإقامة في وحدة العناية المركزة ، مدة الإقامة في المستشفى ، مدة الحاجة إلى التنفس الاصطناعي، حدوث الوفاة لجميع الأسباب،
وحدوث اثار جانبية للعلاج.

Health conditions/problem studied: Specify

COVID-19 and the cardiovascular system
We will aim at treating endothelial dysfunction caused by covid -19 virus by an endothelial protocol to try to improve the patient's outcome

Interventions: Specify

Randomized controlled tiral with 2 arms one intervention arm and the other is a placebo arm

Key inclusion and exclusion criteria: Inclusion criteria

INCLUSION CRITERIA: Firstly, participants must be in-patient adults 18 years of age and above. Secondly, having PCR-confirmed COVID-19 classified as mild, moderate or severe disease as per the FDA and admitted to the hospital for inpatient treatment as per the standard of care, with mild being a positive testing by standard RT-PCR assay or equivalent test and symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea. No clinical signs indicative of Moderate, Severe, or Critical Severity. Moderate defined as positive testing by standard RT-PCR assay or equivalent testing and symptoms of moderate illness which could include any symptom of mild illness or shortness of breath with exertion. Clinical signs suggestive of moderate illness with COVID-19 include respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute without clinical signs indicative of Severe or Critical Illness Severity. Severe symptoms could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical signs indicative of severe systemic illness with COVID-19 include respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300. No criteria for Critical Severity.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

99

Key inclusion and exclusion criteria: Exclusion criteria

EXCLUSION CRITERIA:
Patients unable to tolerate oral medications. Patients who are already on beta-blockers, statins or Nicorandil, PDE5 inhibitors, Riociguat.. In addition to those with shock as defined by SBP<90 for more than 30 minutes not responding to IV fluids with evidence of end organ damage. Patients with severe bradycardia (<50 bpm) and heart block greater than first-degree (except in patients with a functioning artificial pacemaker) should be definitely excluded, along with those who suffer from decompensated heart failure and sick sinus syndrome (unless a permanent pacemaker is in place). Severe hepatic impairment (Child-Pugh class C) or active liver disease are absolute reasons not to be included especially those with unexplained persistent elevations of serum transaminases. Pregnancy or breastfeeding and hypersensitivity to any of the medications are to be excluded as well. Myocarditis. Acute pulmonary edema. Hypovolemia. Patients enrolled in a different randomized study and/or COVID interventional study.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Active

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Lebanon

IMP has market authorization: Specify

Name of IMP

Nicorandil Atorvastatin L-Arginine Folic Acid Nebivolol

Year of authorization

2018

Month of authorization

1

Type of IMP

Others

Pharmaceutical class

Beta blocker
Statin
Dietary supplement
Cornoary vasodilator

Therapeutic indication

Endothelial and Microvascular dysfunction in COVID-19

Therapeutic benefit

1- Scale for clinical improvement
2-Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement)
3- Need for invasive mechanical ventilation
4- Length of ICU stay
5- Length of hospital Stay
6- Length of need of mechanical ventilation
7- All cause mortality
8- Occurrence of side effects

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention
None retained

Biospecimen description
None will be used

Target sample size
66

Actual enrollment target size
80

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
15/11/2020

Date of study closure: Type
Anticipated

Date of study closure: Date
31/12/2020

Recruitment status
Pending

Recruitment status: Specify

Date of completion
01/02/2021

IPD sharing statement plan
Yes

IPD sharing statement description
No personal data will be shared.

Additional data URL
none

Admin comments

Trial status
Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

Name
Self Funding by LAUMCRH

Secondary Sponsors

Name
NA

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Kamal Matli	LAUMCRH	Lebanon	9613439675	matlikamal@gmail.com	LAUMCRH
Scientific	Kamal Matli	LAUMCRH	Lebanon	9613439675	matlikamal@gmail.com	LAUMCRH

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Lebanese American University Medical Center Rizk Hospital	Dr. Georges Ghanem	Cardiology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Lebanese American University- University Medical Center Rizk Hospital	04/01/2021	Karmen Baroudy	karmen.baroudy@lau.edu.lb	01200800

Countries of Recruitment

Name
Lebanon

Health Conditions or Problems Studied

Condition	Code	Keyword
COVID-19	2-Propanol (T51.2)	COVID-19

Interventions

Intervention	Description	Keyword
Medical therapy for COVID-19 infection	Endothelial dysfunction will be targeted by our medications to improve patient outcome in COVID-19 infection	Endothelial dysfunction and COVID-19
Placebo or L-arginine	3g po TID	Supplement
Placebo or Folic Acid	5 mg po OD	Supplement
Placebo or Atorvastatin	40 mg po OD	medication
Placebo or Nicorandil	10 mg po BID	Medication
Placebo or Nebivolol	2.5-5 mg po OD	Medication

Primary Outcomes

Name	Time Points	Measure
Clinical improvement was defined as improvement of at least two points from the baseline from date of intervention administration until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1-month status on the six-category ordinal scale. This scale contains the subsequent categories: (1) death (2) hospital admission requiring invasive mechanical ventilation (3) hospital admission, requiring non-invasive positive pressure ventilation (4) hospital admission, requiring oxygen (5) hospital admission, not requiring oxygen (6) discharge.	we will follow our patients for a total of 28 days .	Clinical Improvement

Key Secondary Outcomes

Name	Time Points	Measure
II.Secondary outcomes: Time Frame: from date of intervention administration until the date of discharge from hospital or date of death from any cause, whichever came first, assessed up to 1 month: Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement) on day 7, 14 and 28 3- Need for invasive mechanical ventilation 4- Length of ICU stay 5- Length of hospital Stay 6- Length of need of mechanical ventilation 7- All cause mortality 8- Occurrence of side effects	we will follow the patients for a total of 28 days	Clinical Endpoint

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files