Clinical Trial Protocol
Iranian Registry of Clinical Trials

04 Feb 2023

Methylene Blue for the Treatment of COVID-19: A Randomized Clinical Trial

Protocol summary

Study aim

To evaluate the effect of intravenous methylene blue on the clinical course and outcomes of patients with COVID-19 infections

Design

This is a parallel design, single center, phase 3, concealed randomized clinical trial study which will be conducted on 260 patients. Patients will be randomized into two groups using an online program available from https://www.sealedenvelope.com/simple-randomiser/v1/lists.

Settings and conduct

This study will be conducted in the Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran. Patient will have 24-hour heart monitoring. In order to minimize any bias between groups as a general policy, all patients will only receive lopinavir/retonavir (Kaletra®) as their treatment regimen for COVID-19.

Participants/Inclusion and exclusion criteria

inclusion criteria: 1. >18 yrs old 2. PCR confirmation of COVID-19 3. Severe or critical diseases as: RR>30 breaths/second, SpO2<94% on room air sea level, lung infiltration of >50%, PaO2/FiO2 <300 mmHg and/or any individual with respiratory failure, septic shock, and/or multiple organ dysfunction exclusion criteria: 1. Pregnancy 2. G6PD deficiency 3. Severe renal failure (defined as GFR<30 mL/min/1.3m2) 4. History of allergic reaction to drug 5. Patients on serotonergic psychiatric drugs (including SSRIs, SNRIs, TCAs, MAOIs), dapsone and different hydroxylamine 6. Organ transplantation recipients 7. Not consenting to enter study

Intervention groups

Intervention group: Kaletra and corticosteroid and methylene blue. Control group: Kaletra and corticosteroid.

Main outcome variables

Death; partial pressure of oxygen/Fraction of inspired oxygen ; Length of intensive care unit stay; In-hospital complications rates; white blood cell count/leukopenia; C-reactive protein levels

General information

Reason for update

Acronym

IRCT registration information

IRCT registration number: **IRCT20090701002113N2**
Registration date: **2020-08-25, 1399/06/04**
Registration timing: **registered_while_recruiting**

Last update: **2020-08-25, 1399/06/04**
Update count: **0**

Registration date

2020-08-25, 1399/06/04

Registrant information

Name

Jamshid Roozbeh

Name of organization / entity

Shiraz university of medical sciences

Country

Iran (Islamic Republic of)

Phone

+98 71 1235 6400

Email address

roozbehj@sums.ac.ir

Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2020-08-15, 1399/05/25

Expected recruitment end date

2020-12-15, 1399/09/25

Actual recruitment start date

empty

Actual recruitment end date

empty

Trial completion date
empty

Scientific title
Methylene Blue for the Treatment of COVID-19: A Randomized Clinical Trial

Public title
Methylene Blue in COVID-19

Purpose
Treatment

Inclusion/Exclusion criteria

Inclusion criteria:
>18 yrs old PCR confirmation of COVID-19 Severe or critical diseases as: respiratory rate>30 breaths/second, oxygen saturation<94% on room air sea level, lung infiltration of >50%, partial pressure of oxygen/Fraction of inspired oxygen <300 mmHg and/or any individual with respiratory failure, septic shock, and/or multiple organ dysfunction

Exclusion criteria:
Pregnancy G6PD deficiency Severe renal failure (defined as glomerular filtration rate<15 mL/min/1.3m2) History of allergic reaction to drug Patients on serotonergic psychiatric drugs (including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake Inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors), dapsone and different hydroxylamine Organ transplantation recipients Not consenting to enter study

Age
From **18 years** old

Gender
Both

Phase
3

Groups that have been masked
No information

Sample size
Target sample size: **260**

Randomization (investigator's opinion)
Randomized

Randomization description
Random allocation (case:control 1:1) will be done using the permuted block randomization method (block size of 4). The randomization sequence will be generated with an online program available from https://www.sealedenvelope.com/simple-randomiser/v1/lists. The generated random sequence will be inserted in an opaque envelop enumerated in sequence from 001 to 260, each of which will be used for consecutive study participants.

Blinding (investigator's opinion)
Not blinded

Blinding description

Placebo
Not used

Assignment
Parallel

Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee

Name of ethics committee
Ethics Committee of Shiraz University of Medical Sciences

Street address
Zand Street

City
Shiraz

Province
Fars

Postal code
7134814336

Approval date
2020-04-05, 1399/01/17

Ethics committee reference number
IR.SUMS.REC.1399.016

Health conditions studied

1

Description of health condition studied
COVID-19 infection

ICD-10 code
U07.1

ICD-10 code description
COVID-19, virus identified

Primary outcomes

1

Description
Death

Timepoint
2 weeks after intervention

Method of measurement
follow-up visit

Secondary outcomes

1

Description
partial pressure of oxygen/Fraction of inspired oxygen

Timepoint
first day of hospital admission, and 1, 3, and 5 days after administration

Method of measurement
By measuring arterial blood gas

2

Description

Length of hospital stay

Timepoint

Daily until discharge

Method of measurement

Daily follow-up visitation

3

Description

ICU admission rate

Timepoint

Daily until the end of hospitalization

Method of measurement

Daily follow-up visitation

4

Description

In-hospital complications rates

Timepoint

Daily until the end of hospitalization

Method of measurement

Daily follow-up visitation

5

Description

White blood cell count/leukopenia

Timepoint

first day of hospital admission, and 1, 3, and 5 days after administration

Method of measurement

By blood test

6

Description

C-reactive protein levels

Timepoint

first day of hospital admission, and 1, 3, and 5 days after administration

Method of measurement

By blood test

Intervention groups

1

Description

Intervention group: In order to minimize any bias between groups as a general policy, all patients will only receive lopinavir/retonavir (Kaletra®) and corticosteroids as their treatment regimen for COVID-19. Antibiotic medications use will be limited as much as possible and will only be used in each specific case based on the diagnosis of the infectious specialist or intensivist when necessary. On the second day of hospital admission, the intervention group will initially receive a single intravenous bolus of 1 mg/kg (1% solution) of methylene blue administered over 20-60 minutes. The patients will then be given 0.25 mg/kg per hour dose of methylene bluefor 24 hours. Methylene blue has a commercial name of METIBLO and generic name of Methylthioninium chloride . Each 1ml ampule contains 10 mg methylthionium chloride. It is made in Belgium by Oterop company.

Category

Treatment - Drugs

2

Description

Control group: These patients will only receive lopinavir/retonavir (Kaletra®) and corticosteroids as their treatment regimen for COVID-19. Antibiotic medications use will be limited as much as possible and will only be used in each specific case based on the diagnosis of the infectious disease specialist or emergency medicine specialist when necessary.

Category

Treatment - Drugs

Recruitment centers

1

Recruitment center

Name of recruitment center

Abu Ali Sina Hospital

Full name of responsible person

Siavash Gholami

Street address

Sadra street

City

Shiraz

Province

Fars

Postal code

71994-67985

Phone

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Email

abualisinacharity@gmail.com

Web page address

https://abualisina.net/%d8%aa%d9%85%d8%a7%d8%b3-%d8%a8%d8%a7-%d9%85%d8%a7/

Sponsors / Funding sources

1

Sponsor

Name of organization / entity

Shiraz University of Medical Sciences

Full name of responsible person

Yunos Ghasemi

Street address

Zand street

City

Shiraz

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71348-14336

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+98 71 3230 5401

Email
info@sums.ac.ir

Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?
No

Title of funding source
Shiraz University of Medical Sciences

Proportion provided by this source
100

Public or private sector
Public

Domestic or foreign origin
Domestic

Category of foreign source of funding
empty

Country of origin

Type of organization providing the funding
Academic

Person responsible for general inquiries

Contact

Name of organization / entity
Shiraz University of Medical Sciences

Full name of responsible person
Jamshid Roozbeh

Position
Professor

Latest degree
Subspecialist

Other areas of specialty/work
Internal Medicine

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Person responsible for scientific inquiries

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Full name of responsible person
Jamshid Roozbeh

Position
Professor

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Person responsible for updating data

Contact

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Full name of responsible person
Jamshid Roozbeh

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Sharing plan

Deidentified Individual Participant Data Set (IPD)
Undecided - It is not yet known if there will be a plan to make this available

Study Protocol
Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan
Not applicable

Informed Consent Form
Undecided - It is not yet known if there will be a plan to make this available

Clinical Study Report
Not applicable

Analytic Code

Not applicable

Data Dictionary

Not applicable