

# 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/lits>.

##### 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, SpO<sub>2</sub><94% on room air sea level, lung infiltration of >50%, PaO<sub>2</sub>/FiO<sub>2</sub> <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/1.3m<sup>2</sup>) 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), dapson 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/lits>. 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 blue for 24 hours. Methylene blue has a commercial name of METIBLO and generic name of Methylthionium

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**  
+98 71 3334 4000  
**Fax**  
+98 71 3643 0038  
**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  
**Province**  
Fars  
**Postal code**

71348-14336

**Phone**

+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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roozbehj@sums.ac.ir

## Person responsible for scientific inquiries

**Contact**

**Name of organization / entity**

Shiraz University of Medical Sciences

**Full name of responsible person**

Jamshid Roozbeh

**Position**

Professor

**Latest degree**

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**Other areas of specialty/work**

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## Person responsible for updating data

**Contact**

**Name of organization / entity**

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**Full name of responsible person**

Jamshid Roozbeh

**Position**

Professor

**Latest degree**

Subspecialist

**Other areas of specialty/work**

Internal Medicine

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+98 71 1235 6400

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**Email**

roozbehj@sums.ac.ir

## 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