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A clinical trial to evaluate the effects of inhaled nitric oxide gas among COVID-19 patients with pneumonia

Submission date
09/03/2021

Recruitment status
No longer recruiting

Registration date
11/03/2021

Overall study status
Completed

Last Edited
11/08/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe. In some patients, this can progress to respiratory failure and patients may need supplemental oxygen or in severe cases, ventilator support to maintain normal oxygen levels. The death rate in patients who need mechanical ventilation to maintain oxygenation is quite high, additionally, ventilator support can lead to secondary infections and expensive healthcare costs.

Effective antivirals that could combat COVID-19 are currently unavailable. Research studies have reported the antiviral and antimicrobial activity of Nitric oxide against pathogens. It can also provide better oxygenation by widening of blood vessels (vasodilation). This trial will explore the effect of inhaled nitric oxide on clinical improvement among patients diagnosed with COVID-19 pneumonia.

Who can participate?
Adult COVID-19 pneumonia patients with respiratory failure due to inability for maintaining appropriate oxygen levels in the blood.

What does the study involve?
Eligible COVID-19 patients will be recruited into the study. Participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin). Participants and researchers will not have a choice in the treatment given. One group will receive standard care only and the other group will receive Inhaled Nitric Oxide using a helmet or tight sealing mask, as pulses lasting for 30 minutes at 12-hour intervals, for 3 consecutive days.

Trained research staff will collect the clinical information of each patient and nasal swabs will be collected on days 3, 5, 7, 10, and 14 post-treatment to estimate the quantity of virus (viral load).

What are the possible benefits and risks of participating?
At the time of writing, there are no proven therapies for this viral disease and if the study drug is effective it could potentially shorten the course and/or severity of the disease in patients. There are no known risks due to study participation.

Where is the study run from?
Amrita Institute of Medical Sciences (India)

When is the study starting and how long is it expected to run for?
From June 2020 to February 2021

Who is funding the study?
Amrita School of Biotechnology (India)

Who is the main contact?
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Contact information

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Public

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Additional identifiers

Study information

Scientific Title
A phase II open-label, randomized, controlled feasibility trial to compare the antiviral activity and clinical efficacy of inhaled nitric oxide gas among COVID-19 patients diagnosed with pneumonia with hypoxic respiratory failure

Study objectives
Nitric oxide increases antiviral activity and reduces hypoxic damage by improved oxygenation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/05/2020, Institutional Ethics Committee Amrita Institute of Medical Sciences (AIMS, Ponekkara, Kochi, Edappally, Ernakulam, Kerala 682041, India; +91 (0)484 2858750; https://www.amritahospitals.org/), ref: IEC/AIMS-2020/CARDANES-044

Primary study design
Interventional

Study design
Prospective phase II open-label randomized controlled feasibility trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Adult COVID-19 pneumonia patients with hypoxic respiratory failure

Interventions
Eligible patients will be randomized into two arms either receiving standard of care only (control arm), or standard of care and inhaled Nitric Oxide (iNO) using a helmet or tight sealing oronasal mask (case arm). iNO will be deluvered as pulses lasting for 30 min at 12 h intervals, for 3 consecutive days. iNO will be administered at the minimum FiO2 to maintain saturations above 92%, using a V60 bilevel positive airway pressure (BiPAP) machine. The flow rates will be titrated to administer escalating doses of iNO starting from 10 ppm to 80 ppm over a period of 30 min. Following this iNO will be weaned off at the rate of 10 ppm per min.

Study patients will be started on oral Sildenafil 10 mg TID for 5 days, to prevent rebound rise in pulmonary pressures after iNO discontinuation, provided their MAP is >60 mmHg. Standard of care therapies including antivirals, steroids, anticoagulants, and other medications will be administered in both study arms as per institutional protocol.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Nitric Oxide gas

Primary outcome(s)
Viral load as defined by cycle threshold measured using Real-Time Polymerase Chain Reaction Surrogate CT ratio from nasopharyngeal swab collected at baseline 3, 5, 7, 10, and 14 days

Key secondary outcome(s)
1. Duration of non-invasive ventilation (NIV) measured from the nursing chart and medical record evaluation recorded at 8 am and 8 pm daily by investigators during the study period collected at end of NIV
2. Duration of oxygen therapy measured from the nursing chart and medical record evaluation recorded at 8 am and 8 pm daily by investigators during the study period collected at end of oxygen therapy
3. Methaemoglobin levels measured using arterial blood gas analysis using a co- oximeter RADIOMETER ABL 800 on blood gas samples drawn after each pulse of iNO therapy at baseline, 1, 2, and 3 days
4. Incidence of methaemoglobin levels >3% during the trial measured using arterial blood gas analysis using a co- oximeter RADIOMETER ABL 800 on blood gas samples drawn after each pulse of iNO therapy at baseline, 1, 2, and 3 days
5. Severe acute respiratory infection (SARI) scale performance assessed during daily rounds by the clinical team collected daily until ICU discharge or achievement of the lowest numeric, whichever is earlier
6. Patient status measured using the Sequential Organ Failure Assessment (SOFA) score from medical chart/investigations obtained at 8 am at baseline and 72 h
7. Length of hospital stay measured from medical chart review on the day of hospital discharge
8. Length of intensive care unit (ICU) stay measured from medical chart review on the day of ICU discharge
9. Deaths measured by investigators for all patients in each arm and followed up daily recorded on the day of death or the immediate day after

Completion date
05/02/2021

Eligibility

Key inclusion criteria

1. Severe acute respiratory infection (SARI) class 4 and 5 (hospitalized with the requirement of oxygen supplementation, high flow oxygen device, or non-invasive ventilation assistance)
2. Respiratory rates <30 and saturating >90% with oxygen or Non-Invasive Ventilation (NIV)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
29

Key exclusion criteria
1. Mental obtundation at ICU admission
2. Contraindications or unwillingness to NIV
3. Requiring mechanical ventilation at ICU admission
4. Pre-enrollment diagnosis of chronic renal failure (CRF) or stage 1 Acute Kidney Injury (AKI) as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines
5. Presence of hemoglobinopathies
6. Shock at presentation (mean arterial pressure <60)
7. History of G6PD deficiency or baseline methemoglobin >3%
8. Presence of baseline pulmonary artery hypertension
9. Pregnancy or breastfeeding

Date of first enrolment
20/09/2020

Date of final enrolment
12/12/2020

Locations

Countries of recruitment
India

Study participating centre
Amrita Institute of Medical Sciences
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682041

Sponsor information

Organisation
Amrita Institute of Medical Sciences and Research Centre

ROR
https://ror.org/05ahcwz21

Funder(s)

Funder type
University/education

Funder Name
Amrita School of Biotechnology

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		31/03/2022	11/08/2022	Yes	No