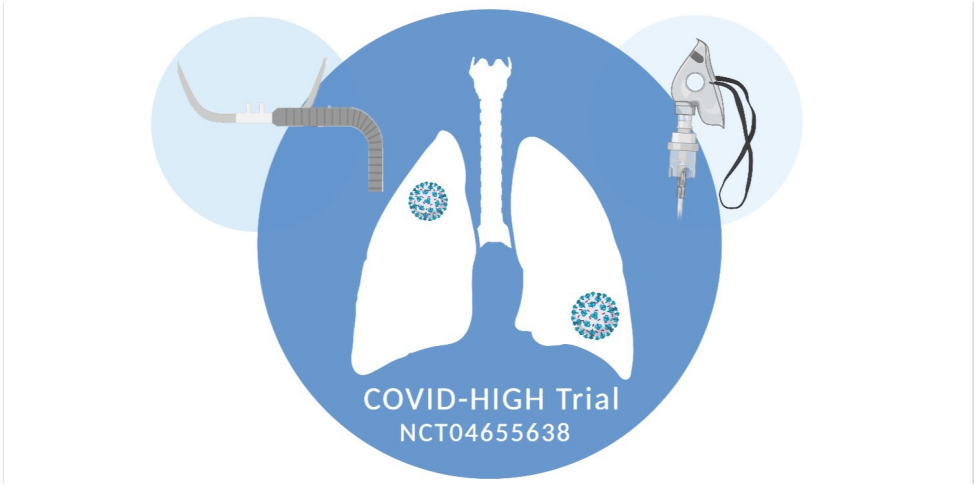

The COVID-HIGH RANDOMIZED CLINICAL TRIAL

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Abstract

The aim of this unblinded parallel-group randomized multicenter clinical trial is to compare the clinical effectiveness of high flow nasal therapy (HFNT) with conventional oxygen therapy (COT) in patients with confirmed COVID-19 related acute hypoxemic respiratory failure.

ClinicalTrials.gov Identifier: NCT04655638

Summary of the protocol

For the purpose of this trial, the interventions will be delivered in any hospital ward caring for COVID-19 patients at the participating centres.

The COVID-HIGH RANDOMIZED CLINICAL TRIAL

Study Type :	Interventional (Clinical Trial)
Sample size:	364 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Unblinded parallel-group randomized multicenter clinical trial
Masking:	Open Label
Primary Purpose:	Treatment
Official Title:	High-Flow Nasal Therapy Versus Conventional Oxygen Therapy in Patients With COVID-19: A Randomized Controlled Trial (The COVID-HIGH Trial)
ClinicalTrials.gov Identifier:	NCT04655638

Table 1. Summary of the protocol

Population

Inclusion criteria to consider patients eligible will be:

- Age ≥ 18 years old
- Tested positive for SARS-CoV-2 using real-time reverse transcriptase PCR (RT-PCR) nasopharyngeal swabs
- Clinical signs of acute respiratory infection and radiological evidence of pneumonia
- Hospital admission in any ward or Emergency Department within 48 h
- SpO_2 ≤ 92% or PaO_2/FiO_2 < 300 in room air and need for oxygen therapy according to clinical judgment, at the screening.

Exclusion Criteria will be:

- PaO_2/FiO_2 ≤ 200
- Respiratory rate ≥ 28 breaths/min and or severe dyspnea and or use of accessory muscles
- Need for immediate intubation or noninvasive ventilation (including CPAP) according to clinical judgment (e.g. clinical diagnosis of cardiogenic pulmonary edema, respiratory acidosis pH ≤ 7.3)
- Patients already on CPAP/NIV or HFNT at study screening
- Septic shock
- Evidence of multiorgan failure
- Glasgow Coma Scale < 13
- Inability to comprehend the study content and give informed consent
- $PaCO_2$ > 45 mmHg, (if blood gas available) or history of chronic hypercapnia
- Patient already on long-term oxygen therapy (LTOT) or home NIV/CPAP (even if only overnight)
- Neuromuscular disease
- Limitation of care based on patients' or physicians' decision

Intervention and comparison

The interventions under investigation will be high flow nasal therapy in comparison with conventional oxygen therapy.

HFNT will be delivered by any device (standalone machine or ventilators able to deliver it). The initial flow rate will be set at 40 L/min and potentially increased up to 60 L/min, according to patient tolerance. Large-bore nasal prongs will be selected according to the size of patients' nostrils (i.e. 2/3 of the diameter of the patient's nostril). A surgical mask will be placed on top of the HFNT interface. The temperature will be set at 37°C or 34 °C according to the patient's comfort. The FiO2 will be adjusted to maintain SpO_2 between 92-96%. A feeding tube or a nasogastric tube will not represent a contraindication for the use of HFNT provided the patency of the used nostril.

Conventional Oxygen therapy will be delivered by any device or combination of devices used for delivering oxygen such as nasal cannula, Venturi Mask or Mask with or without a reservoir bag as per usual local practice. Oxygen flow will be titrated to achieve SpO_2 between 92-96%.

Patients potentially eligible for the study will be evaluated by the attending physicians and receive medical therapy based on the attending physician's decision and local protocols. Awake proning is allowed. Local protocols, including drugs and awake proning, will be discussed with the enrolling centers at the initiation visit, and adherence to WHO guidelines will be recommended. Written informed consent from all the patients will be collected.

Termination criteria & protocol violation

Criteria for weaning off COT or HFNT was at clinical discretion of the managing physician based on the improvement in oxygenation with ability to maintain SpO_2 of 96% or greater with less than 0.30 of FiO_2 or P/F > 300. The switch from COT to HFNT should be considered a protocol violation and should be based on clinical decision of the treating physician.

Criteria to be considered for escalation of treatment: 1) $SpO_2 \leq 92\%$ despite COT or HFNT or P/F ≤ 180 with $FiO_2 \geq 50\%$, and 2) at least one of the following: respiratory rate ≥ 28 breaths/min, severe dyspnea, signs of increased work of breathing (e.g. use of accessory muscles). If the patient meets these criteria, escalation of treatment CPAP, NIV or IMV will be considered.

The choice of the type of escalating treatment will be a clinical decision of the treating physician.

Outcomes

The primary outcome will be the proportion of patients needing escalation of treatment (i.e. noninvasive ventilation - including CPAP - or intubation) during hospital stay.

Secondary outcomes will be i) the proportion of patients needing intubation during hospital stay, ii) the proportion of patients who receive CPAP during hospital stay, iii) the proportion of patients who receive continuous positive airway pressure during hospital stay, iv) the proportion of patients who receive NIV during hospital stay, v) the proportion of patients undergone noninvasive ventilation (e.g. BiLevel, PSV), vi) the proportion of patients admitted to intensive care unit during hospital stay, vii) the proportion of

patients who terminate the study protocols for improvement, viii) length of stay in hospital, ix) time to escalation of treatment to CPAP/NIV during hospital stay, x) time to escalation of treatment to intubation/invasive ventilation during hospital stay, xi) length of stay in ICU, xii) days free from CPAP/NIV during hospital stay, xiii) ventilator-free days during hospital stay, xiv) oxygen-free days during hospital stay, xv) 28-day mortality, xvi) 60-day mortality, xvii) hospital mortality, xix) treatment interruption due to intolerance during study treatment, xx) dyspnea score (BORG scale) during hospital stay [0= no dyspnea to 10= severe dyspnea], xxi) National Early Warning Score 2 (NEWS2) during hospital stay, xxii) ROX index during hospital stay.