DANSK PROTOKOLTILLÆG TIL

Handling oxygenation targets in adults with acute hypoxaemic respiratory failure in the intensive care unit:

A randomised clinical trial of a lower versus a higher oxygenation target (HOT-ICU)

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Introduction

On March 12th 2020, the World Health Organisation declared coronavirus disease 2019 (COVID-19) a global pandemic.[1] On May 28th 2020, more than 5.6 million infected people and 353.334 deaths have been reported globally with many more anticipated.[2] There are no specific therapies for infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and supportive care is the mainstay in the management of these patients.[3] Acute hypoxaemic respiratory failure is the hallmark of hospitalised patients with COVID-19 and the main key factor contributing to a fatal outcome.[4,5] In these patients supplementary oxygen is the most commonly prescribed therapy.[6]

COVID-19 patients acutely admitted to the intensive care unit (ICU) for mechanical ventilation and oxygen therapy fulfil the criteria of acute respiratory distress syndrome (ARDS).[7] In ARDS, the mortality rate is 35-46% depending on severity,[8] however, in COVID-19 patients the mortality rate may be doubled.[4,5,9]

COVID-19 patients acutely admitted to the ICU are eligible in the ongoing multicentre trial, Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU), and since March 2020 a total of 92 COVID-19 patients have been included out of the 2.799 patients randomised so far (see Figure 1). With the expected completion of the HOT-ICU trial in June/July 2020, the number of COVID-19 patients will be too small to draw any conclusions regarding the optimal oxygenation target in this subgroup of ARDS patients.

Due to lack of evidence, the current oxygenation targets in ARDS patients often follows the regimen used in both the conventional and the interventional group in a randomised clinical trial (RCT) published in 2000 aiming to compare higher versus lower tidal volumes; i.e. a partial pressure of arterial oxygen (PaO_2) of 55-80 mmHg (7.3-10.7 kPa) or a peripheral oxygen saturation (SpO_2) of 88-95%.[10] A recently published RCT challenges this postulate as the trial was prematurely stopped due to five cases of intestinal ischaemia, when targeting a lower oxygenation (PaO_2: 7.3-9.3 kPa) compared to none, when targeting a higher oxygenation (PaO_2: 12.0-14.0 kPa).[11] Importantly, myocardial and intestinal ischemia as well as ischaemic stroke are all secondary outcomes in the HOT-ICU trial and were evaluated by the Data Monitoring and Safety Committee (DMSC) at the planned interim analysis, when 1464 patients had passed their 90-day follow-up. We aim to extend the HOT-ICU trial to focus exclusively on COVID-19 patients, being characterised by a specific aetiology and a common presentation, in the HOT-COVID trial.

Aim

To assess benefits and harms of two targets of PaO_2 in guiding medical oxygen administration in SARS-CoV-2 positive patients acutely admitted to the intensive care unit (ICU) with hypoxaemic respiratory failure.

Methods

Study population

This is an amendment to the HOT-ICU trial exclusively for SARS-CoV-2 positive patients. The presence of a positive test for SARS-CoV-2 in any airway secretion or naso-pharyngeal swab prior to the inclusion in the trial is added to the inclusion criteria. Additionally, the fraction of inspired oxygen (FiO_2) criterion for mechanically ventilated patients will be removed, as all mechanically ventilated COVID-19 patients have hypoxaemic respiratory failure.

Inclusion criteria (unchanged is marked in italics)

- *Acutely admitted to the ICU* ***AND***
- *Aged ≥ 18 years* ***AND***
- *Supplemental oxygen with a flow of at least 10 L oxygen per minutes in an open system including high-flow systems OR invasive or non-invasive mechanical ventilation/CPAP systems* independent of the FiO_2 ***AND***
- *Expected to receive supplemental oxygen for at least 24 hours in the ICU* ***AND***
- *Having an arterial line for PaO_2 monitoring* ***AND***
- Confirmed SARS-CoV-2 infection in the time leading to or during current hospital admission

Exclusion

- All exclusion criteria are similar to those specified in the HOT-ICU trial

Outcomes

By changing the primary outcome parameter from 90-days mortality to days alive without life support, the HOT-COVID will be more feasible as a lower number of patients is needed to demonstrate a clinically relevant difference. Importantly, all outcomes are similar to those specified in the HOT-ICU trial.

Primary outcome

- Days alive without life support, i.e. respiratory support, circulatory support or renal replacement therapy (RRT) in 90 days after randomisation (*secondary outcome in main HOT-ICU trial)*

Secondary outcomes

- 90-day mortality (*primary outcome in the main HOT-ICU trial)*
- All other secondary outcomes are similar to those specified in the HOT-ICU trial

Power sample calculation

Given the current knowledge 40% of ICU admitted coronavirus disease 2019 (COVID-19) patients will die while on life support and will thus have 0 days alive and out of life support. Surviving patients will have

estimated 14 days receiving life support out of the 90 days. Therefore, with an average of 45.6 days alive without life support and a standard deviation of 35.0 days, to achieve a maximal type 1 error of 5% and type 2 error of 20% (a power of 80%), a total of 780 patients will be included in the HOT-COVID trial to detect or reject a true absolute increase of 7.0 days in days alive without life support, equal to a 20% mortality reduction (an absolute mortality reduction of 8%-points) and a 10% decrease in days receiving life support in survivors (an absolute decrease of 1.4 days); i.e. estimated 52.6 days alive without life support in the intervention group.

A detailed statistical analysis plan will be published before inclusion of the last patient in the HOT-COVID trial.

Interim analysis

We will conduct one interim analysis when 390 COVID-19 patients (50%) have been followed for 90 days. A blinded DMSC will analyse the primary outcome, the 90-day mortality, and the serious adverse events (SAE) outcome. The DMSC will submit their recommendations to the HOT-ICU Management Committee, which makes the final decision regarding the continuing, pausing or stopping of the trial as described in the charter for the independent DMSC of the HOT-ICU trial.

Time schedule

The HOT-COVID trial will start as soon as the last patient in the main HOT-ICU trial has been included, which is expected to be in June/July 2020. The inclusion period of the HOT-COVID trial is expected to be completed in two years.

Participating sites in the HOT-ICU trial have been invited to continue their participation. Prolongation of contracts and approvals by the authorities will be obtained.

Risks, side effects and disadvantages, and guidelines for oral information and informed consent

The same as in the main HOT-ICU trial as there is no new evidence regarding the two oxygenation targets of a PaO_2 of 8 kPa and a PaO_2 of 12 kPa, respectively, and the regulations regarding informed consent in temporarily incompetent patients have not changed either.

Economy

The primary investigator of the HOT-ICU trial and of the extension HOT-COVID trial, Professor Bodil Steen Rasmussen, Department of Anaesthesia and Intensive Care, Aalborg University Hospital, has initiated the trials. Funding to run the HOT-COVID trial has been granted by the Ministry of Higher Education and Research: 5 mill DDK. None of the researchers involved have financial interests in the trial.

Ethics

The study will provide new important information of the effects of different targets of oxygenation in critically ill SARS-CoV-2 positive patients acutely admitted to the ICU with hypoxaemic respiratory failure.

Publishing of results

All results of the project will be published regardless of the outcomes.

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Figure 1. Overview of HOT-ICU recruitment

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