Statistical Analysis Plan

PRactice of OXYgen Use in COVID–19 patients (PROXY–COVID) – a multicenter observational study

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Objectives

The objective of the study is to compare the amount of supplemental oxygen used with invasive ventilation or noninvasive ventilation (NIV) versus high–flow nasal oxygen (HFNO) in the first 2 days of ventilatory support in patients with acute hypoxemic respiratory failure related to COVID–19.

Hypothesis

The amount of supplemental oxygen used with invasive ventilation or NIV is substantially lower than with HFNO.

Patients

This international study enrolled patients with acute hypoxemic respiratory failure related to COVID–19 that were admitted to the ICUs of two hospitals in the Netherlands and Spain between October 1 2020 and December 31 2020. We excluded patients who received ECMO.

Data collected

- Demographic data and chronic comorbidities were collected at baseline; the Simplified Acute Physiology Score (SAPS) II was calculated using data collected in the first 24 hours after arrival in the ICU. We collected the following data in the first two complete calendar days of ventilation (i.e., ignoring the first calendar day): every 2 hours:
    - supplemental oxygen mode used, i.e., invasive ventilation, NIV or HFNO
    - during invasive ventilation and NIV: ventilation mode, inspiratory tidal volume (V_{Ti}) (L), total respiratory rate (RR), fraction of inspired oxygen (FiO_2) (%), positive end-expiratory pressure (PEEP) (cm H_2O), saturation of

arterial oxygen (SpO_2) (%), partial pressure of arterial oxygen (PaO_2) (kPa), and position (supine or prone)

- during HFNO: FiO_2 (%) air flow (L/min), SpO_2 (%), PaO_2 (kPa), and position (supine or prone)

Definitions

Day 1 and Day 2 are the first two complete calendar days of ICU admission and have a duration of 24 hours (from 00:00 to 23:59). Day 0, defined as the time between ICU admission and 23:59 of that day, is ignored.

Endpoints

The primary endpoint is the amount of oxygen used per minute at patient level.

The secondary endpoints are the total amount of oxygen used and the amount of oxygen used per hour at patient level.

The supplemental oxygen per minute ($Supplemental\ Oxygen_{min}$) is calculated every 2 hours. For invasive ventilation and NIV

$$Supplemental\ Oxygen_{min}\ (L) = V_{Ti}\ (L) * total\ RR * (FiO_2 - 0.21)$$

For the HFNO group

$$Supplemental\ Oxygen_{min}\ (L) = air\ flow\ (L/min) \times (FiO_2 - 0.21)$$

Supplemental oxygen per hour ($Supplemental\ Oxygen_{hour}$) and total supplemental oxygen on Day 1 and 2 are calculated using the area under the curve (AUC) method.

Statistical analysis plan

Continuous data are reported as medians with interquartile ranges and categorical data as numbers with percentages.

Each patient is assigned to a group named ´invasive ventilation or NIV´ and ´HFNO´ based on the first used form of ventilatory support, meaning that patients who received HFNO first and invasive ventilation or NIV afterwards is included in the 'HFNO' group and vice versa.

To assess differences between patient groups in both approaches, Wilcoxon-Mann-Whitney test for continuous data and Fisher exact test for categorical data is used. Differences between demographic data, chronic comorbidities and SAPSII are shown in Table 1. Supplemental oxygen per minute (Supplemental $Oxygen_{min}$) at patient level in the two groups is compared using the Wilcoxon-Mann-Whitney. Cumulative frequency distribution of supplemental oxygen per minute are shown for the two groups.

Supplemental oxygen per minute is compared with repeated measures analysis of variance (ANOVA). If significant, a pairwise comparison between every time points is performed.

Sankey diagrams are used to show the different ventilatory support devices used during Day 1 and Day 2.

Supplemental oxygen per hour (Supplemental $Oxygen_{hour}$) and total supplemental oxygen in the two groups is compared using the Wilcoxon-Mann-Whitney test. Distribution graphs are used to show the differences between the two groups.

In one sensitivity analysis, patients who received both HFNO and invasive ventilation or NIV on Day 1 and Day 2 are excluded, so that patients who received

exclusively HFNO are included in the ‘HFNO’ group and patients who received only invasive ventilation or NIV are included in the ‘invasive ventilation or NIV’ group. For this second approach Baseline characteristics are shown in Table 3.

All analyses are conducted in R Studio v. 4.0.3 (R Foundation, Vienna, Austria) and significance level is set at 0.05.