MAINTAINING A STRICT CONDITION OF NORMOXIA IN INTENSIVE CARE UNIT: RANDOMIZED CONTROLLED TRIAL

BACKGROUND

Oxygen therapy is commonly used in numerous pathological conditions and is essential in the treatment of patients with absolute or relative hypoxia. However, exposure to inhalation of oxygen-rich mixtures (hyperoxic) is recognized as a potential cause of organ damage as well as lung injury (1-4). In vitro and in vivo recent studies on animals and humans identify the mechanisms in which hyperoxia alters the normal cell physiology promoting: the formation of oxygen free radicals, activation of apoptotic pathways, the expression of pro and anti-inflammatory that lead to cell death, and altering the innate immunity by exposing to a higher risk for the development of infections (5-8).

A level or a duration of hyperoxia considered harmful is not determined for the onset of cellular insult as there are no clinical trials on humans that evaluate the appropriate percentage of oxygen considered safe to maintain an adequate tissue oxygen availability. In patients suffering from acute respiratory distress syndrome (ARDS) a number of volumetric and pressure parameters in the ventilation have been studied (9), leading however to the recommendation to use the smallest fraction of inspired oxygen for the maintenance of normoxia (10). Conflicting data have been published on the role of hyperoxia in the onset of postoperative nausea and vomiting, the normalization of oxidative metabolism in patients with brain trauma or stroke, in preconditioning of the ischemia-reperfusion injury in cardiac surgery and the onset of the infection site surgery (SSI) (11-18). The use of oxygen in intensive care unit (ICU) is quite variable and, despite being spread some concern about its possible toxicity, the administration is not regulated, as was demonstrated by a recent Canadian survey in ICUs (19). The toxicity of hyperoxia in patients undergoing mechanical ventilation was the subject of a retrospective study of a recent Dutch study, in which inspiratory fractions of oxygen and high PaO2 values were associated with a higher mortality in ICU (20). However, no prospective clinical trials have evaluated the degree of oxygenation to maintain or the effects of hyperoxia in critically ill patients admitted to ICU (ventilated and not). The frequency of the effects of hyperoxia at the clinical level, although it has been studied in vitro and in healthy volunteers, is therefore not known.

A recent publication describes in detail the mechanisms in which hyperoxia exerts its harmful effects and concludes that the amount of oxygen to be administered should be as low as possible with the aim of preserving tissue oxygenation and calls for a clinical study in order to examine a "hypoxia permissive" or a conservative approach to the administration of oxygen to limit the adverse effects (21).

Following the example of a recent trial (22), the purpose of this study is to assess whether, in critically ill patients, the maintenance of a state of normoxia determine better outcomes in terms of mortality, incidence of organ failure and outbreaks of infections compared to the state of hyper-oxygenation obtained through the conventional oxygen strategy.

MAIN OBJECTIVES

The primary objective of the study is to evaluate if the maintenance of a 'strict' state of normoxia in critical patients, avoiding hyperoxic and hypoxic phases, can result in a reduction of mortality in ICU. Mortality will be assessed for both groups as the number of deaths from any cause that will occur during the ICU stay.

SECONDARY OBJECTIVES

The secondary objectives of the study is to evaluate if the maintenance of a 'strict' state of normoxia in critical patients, avoiding hyperoxic and hypoxic phases, determines:

- a reduction in the onset of organ failure (respiratory, cardiovascular, renal and hepatic) in intensive care
- a reduction in the occurrence of infections in ICU (lung, blood) or in hospital (surgical site). Only microbiologically documented bloodstream and respiratory tract infections were considered.

**TYPE, PHASE, SIZE OF THE STUDY**

The oxygen is a drug widely used in current clinical practice for decades, so it is a Phase IV to evaluate the safety and efficacy of the therapeutic use of this medical gas. The study is single-blind because, after the explanation of the protocol for the informed consent, the patient will not be informed about the doses of oxygen administered and criteria of administration applied, thus ignoring the group of enrolment. Assuming a two-sided alpha level of <0.05 and a power of 80%, we calculated that 330 patients are needed per arm to detect an absolute mortality reduction of 8.0% (relative risk reduction of 40%) compared to 20% mortality observed in patients hospitalized in intensive care for at least three days in 2007.

**OPERATING PROTOCOL**

**Inclusion Criteria**
- patients aged under 18 years,
- patients discharged from the ICU and then re-entered during the study period
- patients enrolled in other prospective studies
- patients with life expectancy of less than 24 hours.

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**Randomization and group management**

On admission, eligible patients will be randomly assigned (by the use of a computerized random number generator in a 1:1 ratio) to a group of liberal conventional oxygen (A) or a group of conservative experimental oxygen (B).

Within the group A patients will receive a fraction of inspired oxygen (FiO₂) aiming to maintain a peripheral oxygen saturation (SpO₂) above 97%, accepting an upper limit of partial pressure of arterial oxygen (PaO₂) of 150 mmHg and a lower limit of 60 mmHg. The blood gas analysis (BGA) control will be taken according to clinical indication. Similarly the decision to Non Invasive Ventilation or intubation and mechanical ventilation will be dictated by common clinical criteria. Consistent with our standard ICU practice, control patients received an FiO₂ of 1.0 during endotracheal intubation, airway suction or hospital transfer.

Patients in Group B will receive a FiO₂ established to maintain SpO₂ between 94 and 98%, or possibly a PaO₂ above 70 mmHg and still less than 100 mmHg. BGA controls will be performed as clinically indicated. It will be given a supplementation of oxygen only if the SpO₂ falls below 94%, while the pre-oxygenation at 100% will not be performed during transport or in anticipation of diagnostic and therapeutic manoeuvres, as above. The clinical criteria will dictate the need: to obtain artificially airway control and to guide the choice about the mode of ventilatory support.

Culture test will be performed on patients as clinically indicated during ICU stay and wards transfer. ICU criteria for diagnosis of infections will adhere to agreed definitions in the reference document drawn up in May 2009 by the Regional Health Agency (23). It will be considered positive for respiratory infections evidence of microbial organisms with more than 1000000 colony forming units (CFU) per millilitre in the case of tracheal aspirates and 10000 CFU/ml in the case of bronchial alveolar lavage. The positive for bacteremia and/or infections related to vascular catheter will be evaluated by blood cultures from peripheral
blood and central venous catheter site if at least in site from 48 hours. The evaluation for surgical site infections will be performed in accordance with standards to date by the CDC in 2009 (24).

Data to be collected in the Case Report Form (CRF)

At the entrance to the ward will be recorded on a special case report form (CRF) (see appendix 1) demographic information (gender, age) and those related to the disease that resulted in the ICU admission, and co-morbidities, history of cancer or kidney failure who determined the severity of the clinical picture, also quantified by the Simplified Acute Physiology Score II (SAPS II) scoring. Data collection will be completed with the acquisition of information about ICU admission regarding the input mode of admission (emergency or programmed), the type of ICU admission (medical, elective surgery, emergency surgery), type of specialized surgery which underwent the study patients, the disease developed during ICU stay, ICU new onset organ failure, type of practice used and duration of their application.

The CRF also provides for the collection of values of PaO2 and FiO2 for each patient at least once a day, where we will get the PaO2/FiO2 ratio required for the definition of respiratory failure. It will also annotated during ICU stay: the duration of ventilatory support in hours, the use of vasoactive amines, the increase of creatinine (> 2.5 mg/dL) and bilirubin (> 4 mg/dl) and use Renal replacement therapy (haemodialysis, continuous veno-venous hemofiltration) subsequent to the first 24 hours of ICU stay, the occurrence of respiratory infections, blood and surgical site developed after 48 hours after ICU admission, ICU LOS and hospital LOS. The primary outcome will be assessed on the basis of all-cause mortality in the ICU. In view of the fact that patients are exposed to the protocol of oxygen only during the ICU stay, and not in the next period of hospitalization in ordinary wards of the hospital (during which the use of oxygen remains quite liberal and at the discretion of the clinical department) or even less at home, it was decided not to extend the monitoring of the survival period after the ICU stay.

Statistical analysis

The assessment of the primary endpoint will be made in the intention-to-treat manner. It intends to make an interim analysis at 12 months (30/11/2010) and then the final analysis at the end of the enrolment period (30/11/2011). Mortality will be assessed for both groups as the number of deaths from any cause that will occur during the ICU stay. The onset of organ failure will be evaluated as a number of new organ failure occurring during hospitalization in ICU. The differences within the groups will be conducted through $\chi^2$ test.

Data ownership and publication

Considering that the aim of the study proposed is to improve the knowledge of the oxygen, the effects of oxygen therapy in critically ill patients and the risk-benefit ratio resulting from the administration of oxygen to patients admitted to intensive care, and that the patients will have freely joined in the belief that the results will be useful for the improvement of care for the diseases from which they are suffering, the investigator agrees on the need to ensure wider publication and dissemination of data in a consistent and responsible way.

Therefore, the promoter of the trial, even under Circ. Min. Health No. 6 of 09.02.02, is obliged to make public the results of the study within 12 months of its completion.

The investigator has the right to present the methods and results of the study at symposia and conferences, and to publish the methods and results of the study and other documents related to the study in scientific journals, theses, dissertations or other publications or presentations.

REFERENCES


ICU PROTOCOL and NURSE ORDER SET

1) ICU ADMISSION
- Complete Inclusion and exclusion criteria check list
- Attribution patient to group A (conventional) or B (restrictive) according to sequential table (table hanging on the closet of the ICU)
- Collect informed consent and place it in the pan on the counter dedicated.
- Write on therapy form (voice O2 therapy): A (conventional); B (restrictive)

2) TREATMENT

Group A – Conventional
- FiO2 established to maintain SaO2 (SpO2) 97-100%
- EGA as clinically indicated
- Upper limit accepted PaO2: 150 mmHg
- Suctioning, bronchoscopy, transport, other manoeuvres: pre-oxygenation and 100% O2 during manoeuvres or as clinically indicated
- Possible intubation or NIV according clinical criteria

Group B – Restrictive
- FiO2 established to maintain SpO2 between 94-98% or PaO2 less than 100 mmHg and, where possible, higher-than 70 mmHg
- increase FiO2 to SpO2 <94%; reduce FiO2 to SpO2 > 98%-
- Suctioning, bronchoscopy, transport, other manoeuvres: no pre-oxygenation and 100% O2 during manoeuvres. Intervene with supplemental O2 if SpO2 <94% as clinically indicated
- Possible intubation or NIV according with clinical criteria
# Oxygen-ICU

## CASE REPORT FORM

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<th>Group and number of randomization</th>
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