The effects of hyperoxia on organ dysfunction and outcome in critically ill patients with SIRS

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1. To study the short- and long-term effect of different target PaO2's on circulatory status, organ dysfunction and outcome.2. To study underlying mechanisms of hyperoxia by determining differences in oxidative stress response between the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44818

Source
ToetsingOnline

Brief title
Hyperoxia and SIRS

Condition

- Other condition

Synonym
systemic inflammatory response syndrome

Health condition

orgaandysfunctie en SIRS

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Hyperoxia, Intensive Care, organ dysfunction, systemic inflammatory response syndrome

Outcome measures

Primary outcome

The primary outcome will be the cumulative delta Sequential Organ Failure

(SOFA) score in the first 14 days).

Secondary outcome

Secondary parameters will include:mean, maximum, delta SOFA score, time spent

in the assigned PaO2 range, hypoxic episodes (PaO2 <55 mmHg), vasopressor /

inotrope requirements, need for renal replacement therapy and fluid balances

(timepoint: first 14 days). Furthermore, oxidative stress parameters

F2-isoprostanes will be determined (on day 1, 2 and 4) and as clinical

endpoints: duration of mechanical ventilation, ventilator-free days, length of

stay (in ICU, in hospital) and mortality (ICU and hospital). Interim analyses

will take place after inclusion of 100 and 250 patients to detect possible

differences in mortality.

Subgroup

To further investigate the circulatory changes due to differences in oxygen

suppletion, we will study additional parameters in a subgroup of patients,

which are too time-consuming to be performed in the whole group. We will

estimate hemodynamics by PICCO (C.I., SVRI, extravascular lung water), microcirculation by sublingual Sidestream Dark Field imaging, and body fluid status and bio-impedance.

Study description

Background summary

Hyperoxia has been encountered in 44% of the patients requiring ventilatory support in the Intensive Care. However, contrary to hypoxia, many physicians do not consider hyperoxia harmful for their patients. To stay away from hypoxia, superfluous administration of oxygen is common practice. Since the pulse oximeter never indicates more than 100%, physicians are often not aware of the unphysiological high PaO2 level. Hyperoxic arterial blood gas values do not commonly cause concern, as physicians lower the FiO2 in only 25% of the observed cases 1.
However, an increasing number of studies not only confirm the well-known negative pulmonary effects of chronic hyperoxia, but also point to more acute circulatory and perfusion effects. In patients with myocardial or cerebral infarction, for example, hyperoxia increases infarct size and mortality. After cardiac arrest, hyperoxia is associated with worse functional outcome and increased mortality.
The underlying mechanisms of hyperoxia's detrimental effects are not clarified. Increased production of reactive oxygen species (ROS), causing oxidative stress, may play a pivotal role, although not all study results are unequivocal. Both animal and human studies suggest that oxidative stress induces systemic vasoconstriction, especially in the microcirculation with a loss of functional capillary density and diminished microvascular flow. This in turn augments systemic vascular resistance and impairs cardiac output. Impaired effective circulating volume and microvascular tissue perfusion will outweigh marginally higher arterial oxygen content (dissolved oxygen hardly contributes to blood oxygen content). Hence, a loss of organ perfusion and oxygen delivery may occur .
However, hyperoxia can also induce several favourable effects, illustrating the need for more clinical and preclinical studies. In patients with severe systemic inflammatory response syndrome (SIRS) with concomitant vasoplegia hyperoxia-induced vasoconstriction may stabilize hemodynamics and reduce the need for intravenous volume resuscitation and vasopressor treatment. Common causes of SIRS in the ICU are trauma, sepsis and ischemia/reperfusion after cardiac arrest or cardiopulmonary bypass. In patients with ischemia/reperfusion hyperoxia-induced vasoconstriction may also exert a preconditioning effect, decreasing myocardial damage and other organ injury. The patients with sepsis

can also benefit from the potential antimicrobacterial properties of hyperoxia, which may also prevent new infections. Furthermore, in patients with haemorrhage, systemic vasoconstriction due to hyperoxia may cause redistribution of blood flow to the vital organs with amelioration of haemorrhagic shock-induced acute kidney injury.

In critically ill patients, a recent retrospective observational study suggested an independent association between both low and high PaO2 with in-hospital mortality, with the nadir of mortality between the 70 and 160 mmHg. However, such studies are subject to many forms of bias, and another retrospective study did not confirm these results. Clearly, prospective trials are needed to search for the optimal pO2 range.
Hence, it is not just the uncertainty of hyperoxia's untoward effects, but also the possibility of some favourable effects that generates the need for prospective studies.

To the best of our knowledge, no prospective clinical studies have shown benefits of supranormal oxygen levels in any subgroup of critically ill patients.
In this study, we will investigate two different oxygenation levels both near to the nadir of mortality as estimated in an earlier retrospective trial, but one being within the natural range and the other in the supranatural range. In critically ill patients with SIRS, we will assess the effect on organ function and circulatory parameters. We will separately analyze the predefined subgroups sepsis, trauma/hemorrhage and post-resuscitation.

Study objective

1. To study the short- and long-term effect of different target PaO2's on circulatory status, organ dysfunction and outcome.
2. To study underlying mechanisms of hyperoxia by determining differences in oxidative stress response between the hyperoxic patients and the normoxemic groups.

Study design

Single blinded, randomized, prospective clinical trial

Intervention

We will investigate 2 groups with pO2 targets both within the range of current practice
Group 1: target PaO2 120 ± 15 mmHg (hyperoxemic)
Group 2: PaO2 75 ± 15 mmHg (normoxemic)

Study burden and risks

The risk and burden for study subjects are small. Placement of central venous catheters and arterial cannulas are part of standard ICU care. Blood sampling is combined with sampling for normal care of patients and will be taken from either the arterial cannula or the central venous catheter. Since the titrated oxygen levels administered to the patients are based on the PaO2 measured in blood and pulse oximetry, and the oxygen levels are within the range of current practice, we do not expose the patients to additional risk. Diaphragm dysfunction will be quantified (and compared between groups) using electromyography (Edi) and ultrasonography (diaphragm thickness, thickening fraction).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Age *18 years
-*2 positive SIRS-criteria:
Temperature >38oC or hypothermia <36oC
Heart rate >90 bpm
Respiratory rate >20 /min or pCO2 <32 mmHg (4.3 kPa)
Number of leucocytes >12 x 109/l of <4 x 109/l of >10% bands
-Within 24 hours of admittance to the ICU
-Expected stay of more than 48 hours as estimated by the attending physician

Exclusion criteria

-Elective surgery
-carbon monoxide poisoning
-Cyanide intoxication
-Methemoglobinemia
-Sickle cell anemia
-Known severe pulmonary arterial hypertension (WHO class III or IV)
-Known severe ARDS (Berlin criteria)
-Cardiac right to left shunting
-Pregnancy
-Severe COPD (Gold class III or IV)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2015
Enrollment:	385
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Conoxia
Generic name:	oxygen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003468-19-NL
CCMO	NL50040.029.14