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Targeted OXYgen therapy in Critical illness

Submission date
05/03/2018

Recruitment status
No longer recruiting

Registration date
07/03/2018

Overall study status
Completed

Last Edited
28/06/2022

Condition category
Respiratory

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The aim of this study is to find out how well specific blood oxygen levels (oxygen saturation) can be maintained for the period of time that each participant is on an artificial ventilator (breathing machine). This is the first part of a future study involving a much greater number of patients which will look at whether there might be a benefit from using a lower target oxygen saturation level compared to normal levels.

Who can participate?
Patients aged 18 and over admitted to the critical care unit requiring artificial ventilation because there is a problem with their lungs

What does the study involve?
The treatment that is being assessed in this study is oxygen; in particular, what the correct dose should be for patients on an artificial ventilator. Participants are randomly allocated into one of two treatment groups: normal blood oxygen levels (control/standard care group) and lower than normal blood oxygen levels (new treatment group). All other aspects of patient care remain the same, it is only the oxygen level in your blood that is altered as a result of the study. Whichever group patients are allocated to, their blood oxygen level is closely watched and maintained within the allocated range. Blood oxygen levels are measured using a device called a pulse oximeter, to give a value called oxygen saturation, which is expressed as a percentage. The highest value is therefore 100% and the normal value in majority of the population is equal or greater than 96%. Levels of 85-100% are tolerated in critically ill patients depending on their illness and background. Participants allocated to the lower oxygen group are maintained at 88-92% throughout the study. If they are allocated into the normal oxygen group, their oxygen saturation is maintained at 96% or more throughout the study. Patients remain in their allocated group for the duration of the study, which is until the breathing tube in their mouths has been removed as part of their standard clinical care. Whilst patients are in the study, a member of the research team collects information from their healthcare records and bedside charts. Blood samples are also taken on the day they begin participating in the study, and then on days 2, 3, 5 and 10 (i.e., five samples in total). After patients have left the critical care unit the research team follows their progress for a maximum of 90 days.

What are the possible benefits and risks of participating?
Patients may choose to withdraw from the study at any point. If they do choose not to continue

in the study they can either allow or not allow the use of the study data already collected. Their involvement in this study does not affect any diagnostic tests or treatments that would impact upon their normal care whilst on the critical care unit. Any alternatives would be decided by the team of doctors looking after them and the research team would not be involved in these decisions. Using oxygen in a more restricted manner may well be beneficial and initial research in this field suggests this to be the case. Understanding more about how a patient's dose of oxygen is related to their survival will hopefully guide doctors in the future. Whilst it may seem strange to suggest that giving less oxygen to critically ill patients may be beneficial, there is a high likelihood this could be true, and has been shown to be so in patients suffering from a heart attack. It is not known which of these two treatment groups will be better for patients, hence the need for this important study. There are no specific advantages or disadvantages from participating. The intervention in this study will be the dose of oxygen patients receive whilst on an artificial ventilator. Oxygen is a drug and is not without side effects, and this study is looking to determine if they can be reduced. The researchers are not aware of any specific harm that may come to patients being in either of the treatment groups. A small study conducted by a previous group of researchers has already demonstrated this. It is not known whether or not a lower blood oxygen level in pregnant women is safe for the unborn child. Pregnant women must not therefore take part in this study. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. The information learned from this study may help us to improve the treatment of critically ill patients needing artificial ventilation in the future.

Where is the study run from?
1. The Royal Free Hospital London (UK)
2. Southampton General Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2017 to November 2019

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Jack Grierson

Contact information

Type(s)
Scientific

Contact name
Dr Jack Grierson

Contact details
Surgical & Interventional Trials Unit (SITU)
Division of Surgery & Interventional Science
Faculty of Medical Sciences| University College London
Charles Bell House (3rd Floor)
43-45 Foley Street

London
United Kingdom
W1W 7JN

Additional identifiers

ClinicalTrials.gov (NCT)
NCT03287466

Protocol serial number
35162

Study information

Scientific Title
A randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients.

Acronym
TOXYC

Study objectives
The administration of high concentrations of oxygen to patients have proved to be harmful in some settings, especially in patients already suffering from damage to their lungs. Patients who require assistance to their breathing with an artificial ventilator due to disease of their lungs are frequently given high concentrations of oxygen to maintain a normal level of oxygen in their blood. It is therefore essential to strike a balance between the benefits and harms of having a normal blood oxygen level. We intend to recruit critically ill patients requiring artificial ventilation into a randomised controlled trial to assess the feasibility of conducting a trial that determines blood oxygen levels.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Harrow Research Ethics Committee, 30/10/2017, REC ref: 17/LO/1334; IRAS number: 217338

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Management of Care, Other

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Lung disease requiring ventilation

Interventions
The randomisation services of Sealed Envelope will be enlisted. TOXYC is a prospective, dual centre, randomised controlled trial. All eligible patients will be randomised to either:
Arm A: The intervention, tightly controlled administration of oxygen to patients to achieve a haemoglobin oxygen saturation (SpO2) of 88-92%.
Or
Arm B: Standard of care, Control, tightly controlled oxygen administration, but to achieve a SpO2 of 96% or above.

This will be a 1:1 randomisation, stratified by site. Randomisation will be done online after consent and registration.
Randomisation schedules will be generated prior to enrolment of the first patient, with access restricted to authorised personnel. Allocation will be held by the Sealed Envelope & UCL Surgical & Interventional Trials Unit.

Doctors and nurses looking after patients in the trial will adjust the amount of oxygen they administer to ensure that the patient's blood oxygen level remains in the allocated target range. Blood oxygen level will be monitored with a standard non-invasive monitor (a pulse oximeter). Feasibility will be assessed by the ease of recruiting complex critically ill patients into a trial of this nature, and the ability of clinical teams to deliver the intervention. A secondary purpose of the study is to look at specific biological markers in blood samples collected from participants, to see if they are associated with clinical outcomes. The information from this study will be used to create a large multi-centre trial to fully evaluate targeted oxygen therapy in critically ill patients.

Intervention Type
Other

Phase
Phase II

Primary outcome(s)
Feasibility, assessed by:
1. Ability to recruit patients at the two sites (recruitment rate), evaluated by monitoring patient screening and subsequent agreement to participate, along with any withdrawal of consent during or after the study
2. Support for the trial from involved clinicians and healthcare workers
3. Rate of withdrawal from both the intervention and control groups
4. Reasons for any withdrawal from the study, assessed by the trial management group at the end of the study to then evaluate whether the protocols were suitable
5. Implementation of targeted oxygen, evaluated by analysing adherence to oxygenation goals and completion of intervention without protocol violations

Key secondary outcome(s)
Measurements of oxidative stress markers in blood samples taken from participants on days 2, 3, 5 and 10 to understand the underlying biological mechanisms that link blood oxygen levels to clinical outcomes. Routine clinical data and outcome measures will be collected from the participants in order to assess the safety of the intervention. These can be summarised as:
1. Respiratory measurements: arterial blood gases, oxygen saturation, fraction of inspired oxygen, ventilator measures and settings, time to extubation/detachment from mechanical ventilation and mechanical ventilation free days on ICU

2. Cardiovascular measurements: blood pressure, heart rate, cardiac rhythm, vasopressor / inotrope doses, daily fluid balance, inotrope/vasopressor free days on ICU
3. Renal measurements: creatinine, daily fluid balance the need for renal replacement therapy, and renal replacement therapy free days on ICU
4. Hepatic measurements: transaminases, blood clotting values and bilirubin
5. Blood lactate
6. Adverse events
7. Sequential Organ Failure Assessment (SOFA) score change
8. Acute Physiology and Chronic Health Evaluation (APACHE) II score
9. Length of ICU stay
10. Length of hospital stay
11. 30 and 90 day mortality rates, and days alive out of hospital
Most measures will be taken daily, except for those specifically related to oxygenation, which will be collected hourly, to permit detailed analysis of compliance to blood oxygenation target

Completion date
30/11/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 29/11/2018:
1. Unplanned admission to a critical care unit
2. 18 years of age and above (no upper age limit)
3. Respiratory failure forms part of the admission diagnosis
4. The patient is mechanically ventilated via an endotracheal tube
5. The patient is expected to receive mechanical ventilation for > 24 hours
N.B. In the TOXYC trial, the trigger for inclusion is at the point of intubation and not at admission. E.g. A subject that is admitted but not intubated is not eligible but a subject who deteriorates to the point of requiring intubation and is then intubated then becomes eligible. Once a subject is intubated, site has 24 hours to gain the appropriate consent, enrol and randomise the subject, should site chose to

Previous inclusion criteria:
1. Unplanned admission to a critical care unit
2. 18 years of age and above (no upper age limit)
3. Respiratory failure forms part of the admission diagnosis
4. The patient is mechanically ventilated via an endotracheal tube
5. The patient is expected to receive mechanical ventilation for > 72 hours
N.B. In the TOXYC trial, the trigger for inclusion is at the point of intubation and not at admission. E.g. A subject that is admitted but not intubated is not eligible but a subject who deteriorates to the point of requiring intubation and is then intubated then becomes eligible. Once a subject is intubated, site has 24 hours to gain the appropriate consent, enrol and randomise the subject, should site chose to

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Admission following surgery (elective or unplanned)
2. Those patients expected to die within 24 hours of admission to ICU *
3. Pregnant females
4. Admission post-cardiac arrest
5. Patients with chronic lung disease known (or highly suspected) to have baseline oxygen saturations in the range of the intervention arm (i.e. 88-92%)
6. Admission post trauma (including traumatic brain injury)
7. Known sickle cell trait or disease
8. Ongoing significant haemorrhage or profound anaemia
9. Severe peripheral vascular disease
10. Severe pulmonary hypertension
11. Other medical conditions where mild hypoxaemia would be contraindicated **
12. Patients participating in other interventional clinical trials
* As determined by the responsible clinical team
** As determined by the responsible clinical team and/or research team

Date of first enrolment
15/02/2018

Date of final enrolment
30/11/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal Free Hospital London (lead centre)
United Kingdom
NW3 2QG

Study participating centre

Southampton General Hospital
United Kingdom
SO16 6YD

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-0815-20006

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. All data will be handled in accordance with the UK Data Protection Act 1998. The Electronic Case Report Forms (eCRFs) will not bear the subject's name or other personal identifiable data. The subject identifier and subject number, will be used for identification. This study will use an eCRF. All data will be entered in the approved TOXYC database by a member of the TOXYC study team and protected using established procedures. Access to the eCRF system will only be provided to staff with relevant authority delegated to them on the site's delegation log. Coded data: Participants will be given a unique study Subject Number. Data will be entered under this identification number onto the central database stored on the servers. The database will be password protected and only accessible to members of the TOXYC study team, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access. The database software (MACRO https://macro.ctg.ucl.ac.uk/macro) provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data. After completion of the study the database will be retained on the servers of UCL for ongoing analysis of secondary outcomes. The screening log, linking patient identifiable data to the pseudo-anonymised subject number, will be held locally by the study site. This will either be held in

written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the study the screening log will be stored securely by the sites for 20 years unless otherwise advised by Sponsor.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/01/2019	28/06/2022	Yes	No
HRA research summary			28/06/2023	No	No