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Clinical paper

The EXACT protocol: A multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients

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Abstract

Background: Experimental and observational research suggests hyperoxia following resuscitation from cardiac arrest is associated with neurological injury and worse clinical outcomes. This paper describes the rationale and design of the EXACT trial. EXACT aims to determine whether reducing oxygen in the acute phase of post-resuscitation care for out-of-hospital cardiac arrest (OHCA) improves survival.

Methods: EXACT is a multi-centre, randomised (1:1), single-blind, parallel trial. Presumed cardiac OHCA cases who achieve a return of spontaneous circulation will be eligible if they are comatose, with an advanced airway and have an oxygen saturation (SpO_2) $\geq$95% on $>$10 L/min (or 100% oxygen). Paramedics will randomise 1416 eligible cases to receive oxygen therapy targeting an SpO_2 of 90–94% (intervention) or 98–100% (control). Study treatment will continue until admission to an intensive care unit or hospital ward. The primary outcome is survival to hospital discharge. Secondary outcomes include 12-month survival and quality of life.

Results: The study has commenced in the Australian states of Victoria and South Australia, and has enrolled 167 eligible cases to date (80 intervention and 87 control). Further sites are due to commence in 2019, recruitment is expected to take three years.

Conclusion: This study will determine if early reduction of oxygen leads to improved outcomes in OHCA. Such a finding may potentially change clinical practice with implications on future OHCA survival outcomes.

Trial registration number: NCT03138005.

Keywords: Oxygen, Hyperoxia, Out-of-hospital cardiac arrest, Heart arrest, Post-resuscitation care

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https://doi.org/10.1016/j.resuscitation.2019.04.023
Received 19 December 2018; Received in revised form 3 April 2019; Accepted 10 April 2019

Introduction

Background

Out-of-hospital cardiac arrest (OHCA) is common and carries a high mortality rate. For example in our region of Australia and New Zealand, there are approximately 25,000 OHCAs per year with only 12% surviving.[1] Post-resuscitation care forms an important link in the chain of survival in these patients, but some guideline recommendations,[2,3] such as the delivery of oxygen, are based on weak evidence.[4]

Currently, in patients who achieve a return of spontaneous circulation (ROSC), paramedics routinely administer 100% oxygen during transport to hospital. This high oxygen delivery often continues for hours in the emergency department (ED), during cardiac catheterisation (if undertaken), and into the intensive care unit (ICU). Once admitted to the ICU, the fraction of oxygen (FiO_2) on the ventilator is then decreased to target a partial pressure of oxygen (PaO_2) level within the normal range (generally a PaO_2 of >70 mmHg and an oxygen saturation (SpO_2) >94%).

Experimental and clinical evidence

The use of 100% oxygen for the first hours after resuscitation is largely one of tradition, based on the notion that several hours of hyperoxia might be beneficial in a patient who has suffered profound tissue hypoxia and may also prevent further hypoxic episodes. However, systematic reviews from laboratory studies[5] and observational clinical studies[6] suggest that the administration of 100% oxygen in the hours after ROSC may increase mortality and neurological injury. The largest observational study in humans found only 19% were normoxic on arrival at ICU, and hyperoxia was independently associated with increased in-hospital mortality.[7]

Given current evidence on the pathophysiology of reperfusion injury, it is theoretically plausible that hyperoxia may cause biological harm.[8] In the early period of reperfusion after resuscitation from cardiac arrest, there is a cascade of molecules produced that are known to injure neurones (reperfusion injury). Whilst reperfusion injury mechanism is complex, one of the major contributors to this injury is the generation of oxygen free-radicals, which are further increased by the administration of additional supplemental oxygen.[9]

Pilot study

One issue for the delivery of normoxia in the pre-hospital setting is the accurate titration of oxygen using available equipment. Many EMS insert supraglottic or endotracheal airways during or immediately after OHCA. Ventilation is provided manually using a bag and reservoir with supplemental oxygen at (or above) 10 L/min.

To examine the impact of reducing oxygen on patient oxygenation, we conducted a pilot study to test whether prehospital titration of oxygen results in an equivalent number of patients arriving at hospital with a $SpO_2 \geq 94\%$ (NCT02499042).[10] We randomised 61 patients to titrated (2–4 L/min, approximately 40–70% oxygen[11]) oxygen or control (≥10 L/min, i.e. 100% oxygen[11]). Patients allocated to titrated oxygen were more likely to desaturate (SpO_2 <94%: 43% vs. 4%, p = 0.001; SpO_2 <90%: 19% vs. 4%, p = 0.09); however, the majority (81%) of these desaturations occurred at 2 L/min. On arrival at hospital the majority of patients had a $SpO_2 \geq 94\%$ (titrated: 90% vs. control: 100%) and all patients had a $SpO_2 \geq 90\%$. These data suggested that oxygen titration post-ROSC is feasible in the prehospital environment, but needs to occur incrementally.

Objectives and design

This paper describes the rationale and design of the EXACT trial (acronym for Reduction of Oxygen After Cardiac Arrest). The EXACT trial is designed as a randomised, controlled, patient-blinded multi-centre trial with two parallel groups and a primary endpoint of survival to hospital discharge. The primary objective of EXACT is to determine whether reducing oxygen in the acute phase of post-resuscitation care for OHCA improves survival. Secondary objectives of the trial are to evaluate the effects of targeted oxygen on cardiac and neurological outcomes, and quality of life at 12-months (Table 1).

Methods

Trial summary

The EXACT trial is funded in Australia by the National Health and Medical Research Council (NHMRC). The study commenced in Victoria (at Ambulance Victoria and 13 hospitals in Melbourne),

Table 1 – Outcomes.

Primary outcome
Survival to hospital discharge.
Secondary outcomes
Recurrent cardiac arrest requiring chest compressions before ICU admission and not related to withdrawal of life-sustaining treatment
Myocardial injury (cardiac biomarkers, echocardiogram and ST-resolution by 24 h in those with STEMI)
Incidence of hypoxia ($SpO_2 < 90\%$) before ICU admission
Neurological outcome (Cerebral Performance Category score) at hospital discharge.
Survival to intensive care unit discharge
Intensive care unit and hospital length of stay
Cause of death during hospital stay (e.g. cardiogenic shock, re-arrest with no ROSC, treatment withdrawn — hypoxic brain injury, brain death)
Quality of life (SF-12 and EQ-5d), neurological outcome (modified Rankin Score), degree of recovery (GOS-E) and survival at 12-months

Australia, on the 11th of December 2017, and has currently enrolled 167 eligible patients (80 intervention and 87 control). To date, there have been 7 protocol deviations due to the enrolment of ineligible patients. South Australia commenced on March 26th 2019. Other Australian and international ambulance services are expected to commence in late 2019, the study is expected to take four years to complete (including 12-month follow-up). A list of study sites is available from EXACT investigators. The roles and responsibilities of the EXACT Committees are given in Supplementary Table S1. The study is registered at https://clinicaltrials.gov (NCT03138005).

Eligibility criteria

Inclusion and exclusion criteria are given in Table 2.

Randomisation, allocation and blinding

Patients will be enrolled by attending paramedics trained in the study protocol. These paramedics will determine if the patient is eligible, open a trial envelope and provide pre-hospital trial treatment as per the randomisation card. Randomisation cards, which include a study number and details of the study intervention, are sealed within an opaque envelope.

Trial treatment has been allocated 1:1 in blocks of 10 as per a computer generated randomisation schedule. The schedule was generated by an investigator and is kept securely at Monash University. Randomisation will be stratified by each ambulance service to control for possible differences in paramedic and hospital treatments. It is not feasible to blind paramedics and hospital staff treating the patient. Data collectors will also not be blinded as documented treatment is likely to reflect allocation. However, patients, the study statistician and 12-month data collectors will be blinded to treatment allocation.

Study treatments

Study treatments will begin pre-hospital and continue until hospital ward or ICU admission. A trial summary is provided in Fig. 1, and full details, including contingencies for extubation and reintubation, are given in the Supplementary materials.

Immediately after ROSC, the patient will receive the current standard of care (100% oxygen or $\geq$10 L/min) until a satisfactory SpO_2 trace and reading is achieved.

Patients allocated to "target SpO_2 98–100%" will continue to receive $\geq$10/L minute or 100% oxygen setting if mechanically ventilated. This treatment will continue to patient handover in the ED. On ED handover, enrolled patients will continue on the pre-hospital oxygen level until connected to a ventilator. The oxygen setting may then be decreased provided SpO_2 is maintained between 98–100%.

Patients allocated to "target SpO_2 90–94%" will have oxygen reduced initially to 4 L/min (i.e. approximately 70% oxygen) or an air mix setting if mechanically ventilated. If the SpO_2 remains $\geq$94% for 5 min and the patient is being manually ventilated, the oxygen flow rate will be further reduced to 2 L/min (i.e. approximately 46% oxygen) to target an SpO_2 of between 90–94%. After ED handover, oxygen will be titrated to maintain a target oxygen saturation of 90–94%.

The oxygen flow will be immediately increased to $\geq$10/L minute or a FiO_2 of 1.0 (i.e. 100%) if: the oxygen saturation falls to <90% at any time; recurrent cardiac arrest occurs; or if the pulse oximeter trace fails to read despite correct placement.

To identify allocation group a plastic adhesive tag will be connected to the airway device to enable the treatment allocation to be readily visible to treating doctors and nurses in the ED after hospital arrival. This tag will not obstruct the visualisation of the airway device and will be removed after arrival in ICU.

The management of all patients in the pre-hospital phase will follow standard post ROSC care such as continual assessment, blood pressure management, 12 Lead ECG, blood glucose monitoring, treating possible causes of the OHCA and notification to the receiving hospital.

The management of all patients after ED arrival and hospital admission will follow the hospital's standard practices for OHCA management. Typically these include carbon dioxide control, blood pressure control and targeted temperature management. If patients are transferred between participating hospitals, study allocation will continue as per protocol.

Patients transferred to the cardiac catheterisation laboratory will continue to follow oxygen titration treatment as per study allocation ("target SpO_2 98–100%" or "target SpO_2 90–94%").

Table 2 – Inclusion and exclusion criteria.

Inclusion criteria
Adults (age 18 years or older)
Out-of-hospital cardiac arrest of presumed cardiac cause
All cardiac arrest rhythms
Unconscious (Glasgow Coma Scale <9)
Return of spontaneous circulation
Pulse oximeter measures oxygen saturation at $\geq$95% with oxygen flow set at >10 L/min or FiO_2 at 100%
Patient has an ETT or SGA and is spontaneously breathing or ventilated
Transport is planned to a participating hospital
Exclusion criteria
Female who is known or suspected to be pregnant
Dependent on others for activities of daily living (i.e. facilitated care or nursing home residents)
"Not for Resuscitation" order or Advanced Care Directives in place
Pre-existing oxygen therapy (i.e. for COPD)
Cardiac arrest due to drowning, trauma or hanging

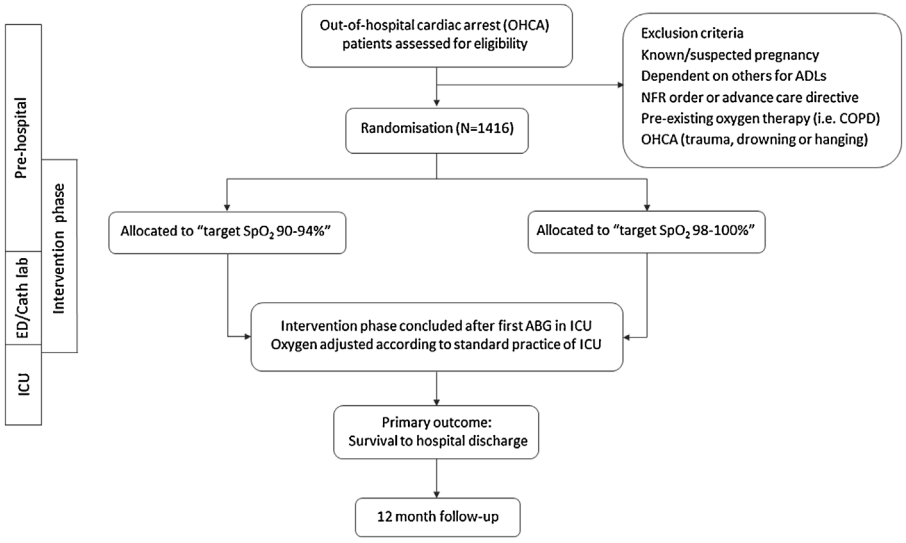

Fig. 1 – Outline of the EXACT trial.

After arrival in the ICU, the patient will continue on the allocated oxygen treatment until the initial ICU ABG is taken. After this point the intervention phase of the study is concluded and the oxygen treatment will follow the standard practice of the ICU. All subsequent management of the patient is at the discretion of the treating ICU physician.

One-year follow-up

Australian patients surviving to hospital discharge will be contacted by experienced staff at the Study Coordinating Centre (Monash University) 12 months after recruitment. The staff conducting follow-up calls will be blinded to the treatment allocation. Patients or a proxy (i.e. family member) will be invited to provide verbal consent and participate in a telephone interview using the 12-Item Short Form Health Survey (SF-12),[12] EuroQol (EQ-5D™) health questionnaire,[13] Glasgow Outcome Scale-extended (GOSE)[14] and modified Rankin Score (MRS).[15]

Sample size

The data from the Victorian Ambulance Cardiac Arrest Registry (VACAR) found that for the year 2013–2014 of the OHCA patients who had ROSC, 35% of those survived to hospital discharge.[16] In the RICH trial,[17,18] there were 397 patients enrolled and 134 (34%) survived to hospital discharge. Given that the largest observational clinical study found that hyperoxia had a odds ratio of 1.8 for mortality compared with normoxia, (8) and the two meta-analyses of the observation studies had odds ratio of 1.4 for improved outcome with normoxia,[6,19] the sample size for this trial will be powered to detect a much more modest relative improvement in outcome of 25%. The 100% oxygen arm is predicted as having 35% survival rate and the targeted oxygen arm is planned to have 44% survival rate. After adjusting for the interim analysis, the study requires 643 patients per arm with 90% power and restricted $\alpha = 0.049$. We plan to add 10% to this sample size to account for loss to follow up. The overall planned enrolment size will therefore be 1416 patients. The study is expected to take four years to recruit.

Recruitment

Each ambulance service will monitor attended OHCA patients for missed enrolment and discuss each case with treating paramedics. Newsletters will be sent out regularly to paramedic teams with updates and reminders.

Data management

All pre-hospital and in-hospital patient data will be collected into a secure online database (REDCap). The REDCap database will be hosted on Monash University managed servers in a secure datacentre in Victoria, Australia. All data is encrypted in transit using industry's standard SSL encryption. Data is backed up nightly and backups are securely stored at a geographically distinct location in Victoria, Australia.

Pre-hospital data will be collected from each ambulance service's cardiac arrest registries and ambulance patient care records (PCRs). In-hospital data will be collected retrospectively from the enrolled patient's hospital medical record by trained data collectors using a standardised data dictionary (available from authors). Data includes sociodemographics (e.g. age, sex), arrest features (e.g. witnessed, duration in arrest), pre-hospital clinical data (e.g. airway type, desaturations, and treatments), hospital clinical data (e.g. post-arrest treatments, desaturations), adverse events (e.g. re-arrest during a desaturation) and outcomes (e.g. survival to hospital discharge, neurological outcomes). Due to the large number of sites and available funding, auditing will only occur for participants who experience a serious adverse event.

Final data will be stored at Monash University on a secure password protected server. The server on which the data will be stored will require active directory permissions and will be restricted to the study staff at the Study Coordinating Centre. All data transfers will be via a Secure File Transfer Protocol (SFTP) using Secure Socket Layer (SSL) 128bit encryption. Data transfer, storage and access protocols meets the International (and Australian) ISO27,001 standard for information security.

Statistical methods

Interim analysis

One blinded interim analysis will be conducted and reviewed by the Data Safety Monitoring Committee (DSMC) after 50% of participants have been enrolled. The DSMC can request unblinding of data if required. In order to control the overall type I error rate, we will set the alphas using the O'Brien-Fleming approach, such that the $\alpha 1 = 0.0054$, and $\alpha 2 = 0.0492$. Sample size has been adjusted (increased by 3 cases in each arm) to account for the interim analysis.

The study will be discontinued at the interim analysis if there are safety concerns related to a group difference in serious adverse events; a survival to hospital discharge difference between the two arms using a strict p-value ($p < 0.005$) according to the O'Brien-Fleming rule; and results from other published studies show benefit or harm with any of the interventions.

The principal trial analyses of primary and secondary outcomes will be conducted on an intention-to-treat basis (all randomised patients excluding those withdrawing consent for data collection) and in the per-protocol sample (all randomised patients excluding those withdrawing consent and protocol violations). Data analysis will be performed independently by a statistician who is blinded to the allocated intervention arms.

Analysis of the primary and secondary outcomes will be performed using the chi-square test for binary outcomes and *t*-test for continuous outcomes. Non-parametric variables will be summarised as median $\pm$ interquartile range, and groups compared using Mann-Whitney Rank sum tests. Kaplan-Meier methods will be used to assess 12-month survival according to randomisation assignment. Multivariable analysis of outcomes using logistic or linear regression will be used if there is variation in baseline characteristics. Included co-variates will be determined a priori by the Steering Committee. A detailed statistical plan will be published with the final manuscript. All reported P values will be two-sided.

Subgroup analyses

Primary and secondary outcomes analysis by treatment group will also be examined in the following a priori subgroups: age $\geq$65years; sex; witnessed arrest; bystander CPR; witnessed and bystander CPR; initial shockable and non-shockable rhythms; collapse to ROSC $>$ 20 min; use of drugs for airway insertion; and ambulance service, and for specific aetiologies such as those with and without acute coronary syndromes. Adjusted subgroup analyses will performed using multivariable logistic regression.

Data monitoring

A DSMC comprising experts in clinical trials, biostatistics, emergency and cardiac medicine has been established. The DSMC will monitor accumulated data periodically during the recruitment phase and report to the Steering Committee accordingly. The DSMC will subsequently make recommendations to the steering committee regarding the continuation, termination, or proposed modifications to the study based on the observed effects of the study intervention and adherence to the study protocol. Unless the DSMC request cessation of the trial the Steering Committee will not be informed of results of interim analyses performed by the DSMC.

Ethics and consent

The study protocol was originally approved by the Alfred Hospital Human Research Ethics Committee (in Victoria). Protocol modifications will be approved by the Alfred Ethics Committee before approval at other site Ethics Committees.

Consent in Australia

Patients who are eligible for this study will be unconscious following resuscitation after a cardiac arrest and will be unable to provide informed consent. In Australia, the NHMRC Ethics Statement makes provision for delayed or waiver of consent in time-critical interventions within the emergency or critical care setting. There is also a different legal framework in each Australian state allowing for delayed or waiver of consent for research in emergency situations. Justifications for deferred or waived consent in this trial include the requirement for treatment to be administered pre-hospital immediately after patient resuscitation (see Supplementary materials). In Victoria and South Australia, where the study has commenced, the study is approved under a waiver of informed consent. In Victoria, a letter is sent to survivors or families informing them of enrolment and the option to withdraw data (details and rationale provided in Supplementary materials). A similar delayed process has been used in previous Victorian cardiac arrest trials (e.g. RINSE[20] in which 0.3% [4/1202 cases] of cases withdrew data), with only a small number of complaints from those contacted.

The approach to consent in other regions participating in EXACT will be based on the recommendations of regional ethics committees. Consent procedures for other study regions will be reported in the main trial publication.

Confidentiality

Patients will be enrolled at the pre-hospital stage and allocated a study number. The study number will be used for the collection of all trial data. The patients name, address, phone number and study number will be kept on a separate spreadsheet within each State Study Site — this information is required for study tracking, to send the patient information sheet to patients discharged alive, and for the 12-month follow-up.

Discussion

Previous systematic reviews[5,6] and recent preliminary clinical data[21,22] suggests targeting a normal level of oxygen, as opposed to a hyperoxic state, is associated with improved outcomes for OHCA patients. However, the existing level of evidence is not of sufficient quality to definitively change clinical practice.[4]

The International Liaison Committee on Resuscitation (ILCOR) review in 2010 notes that "There is insufficient clinical evidence to support or refute the use of inspired oxygen concentration titrated to arterial blood oxygen saturation in the early care of cardiac arrest patients following sustained ROSC.".[23] The review also identifies the need for prospective randomized controlled clinical trials to compare ventilation with 100% oxygen versus ventilation with inspired oxygen titrated to an arterial blood oxygen in the period after sustained ROSC. The recent 2015 ILCOR review, states that the existing evidence relating to treatment with hyperoxia vs. normoxia post-arrest is of "very low quality"—which is the lowest ranking possible for evidence quality and again identifies the need for high-quality RCTs.[4]

Conclusion

The EXACT study will determine if early reduction of oxygen leads to improved outcomes in OHCA. Such a finding may potentially

change clinical practice with implications on future OHCA survival outcomes.

Funding

The EXACT study is funded by a project grant from the National Health and Medical Research Council (NHMRC; #GTN1107509). The Pre-hospital Emergency Care Australia and New Zealand (PEC-ANZ) NHMRC Centre of Research Excellence (#GTN1029983) will supply infrastructure and administrative support. JB and DS are supported by Heart Foundation Fellowships. PC is funded by a NHMRC Fellowship. The funders had no role in the trial design, or in the writing of the manuscript.

Conflicts of interest

None.

Acknowledgments

We would like to acknowledge Dr Dhanya Nambiar for her contribution.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.023.

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