Resuscitation 85 (2014) 1686–1691

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): A randomised controlled feasibility trial☆

Paul Young[a,b,*], Mark Bailey[c], Rinaldo Bellomo[d,e], Stephen Bernard[f], Bridget Dicker[g], Ross Freebairn[a,h,i], Seton Henderson[a,j], Diane Mackle[a,b], Colin McArthur[a,e,k], Shay McGuinness[a,e,k], Tony Smith[g,k], Andrew Swain[b,c], Mark Weatherall[a,b,l], Richard Beasley[a,b]

[a] Medical Research Institute of New Zealand, PO Box 7902, Wellington, New Zealand
[b] Wellington Hospital, Capital and Coast District Health Board, Private Bag 7902, Wellington, New Zealand
[c] Wellington Free Ambulance, PO Box 601, Wellington, New Zealand
[d] Intensive Care Unit, Austin Hospital, PO Box 5555, Heidelberg, 3084 Victoria, Australia
[e] Australian and New Zealand Intensive Care Research Centre, The Alfred Centre, Level 6 (Lobby B), 99 Commercial Road, Melbourne, 3004 Victoria, Australia
[f] Alfred Hospital, 55 Commercial Road, Melbourne, 3004 Victoria, Australia
[g] St John Ambulance, 2 Harrison Road, Private Bag 14902, Panmure, Auckland, New Zealand
[h] Hawke's Bay Hospital, Omahu Road, Private Bag 9014, Hastings, New Zealand
[i] Chinese University of Hong Kong, Sha Tin, Hong Kong, China
[j] Christchurch Hospital, 2 Riccarton Avenue, Christchurch, New Zealand
[k] Auckland City Hospital, 2 Park Road, Grafton, Auckland, New Zealand
[l] University of Otago, School of Medicine, PO Box 7343, Wellington South, Wellington, New Zealand

ARTICLE INFO

Article history:
Received 27 July 2014
Received in revised form 27 August 2014
Accepted 2 September 2014

Keywords:
Oxygen therapy
Hyperoxia
Cardiac arrest

ABSTRACT

Aims: To investigate the feasibility of delivering titrated oxygen therapy to adults with return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest (OHCA) caused by ventricular fibrillation (VF) or ventricular tachycardia (VT).
Methods: We used a multicentre, randomised, single blind, parallel groups design to compare titrated and standard oxygen therapy in adults resuscitated from VF/VT OHCA. The intervention commenced in the community following ROSC and was maintained in the emergency department and the Intensive Care Unit. The primary end point was the median oxygen saturation by pulse oximetry (SpO_2) in the pre-hospital period.
Results: 159 OHCA patients were screened and 18 were randomised. 17 participants were analysed: nine in the standard care group and eight in the titrated oxygen group. In the pre-hospital period, SpO_2 measurements were lower in the titrated oxygen therapy group than the standard care group (difference in medians 11.3%; 95% CI 1.0–20.5%). Low measured oxygen saturation (SpO_2 < 88%) occurred in 7/8 of patients in the titrated oxygen group and 3/9 of patients in the standard care group ($P = 0.05$). Following hospital admission, good separation of oxygen exposure between the groups was achieved without a significant increase in hypoxia events. The trial was terminated because accumulated data led the Data Safety Monitoring Board and Management Committee to conclude that safe delivery of titrated oxygen therapy in the pre-hospital period was not feasible.
Conclusions: Titration of oxygen in the pre-hospital period following OHCA was not feasible; it may be feasible to titrate oxygen safely after arrival in hospital.

1. Introduction

Despite oxygen being a ubiquitous therapy in patients resuscitated from out-of-hospital cardiac arrest (OHCA), there is little high quality evidence to guide clinicians about how best to use oxygen in this patient group. With the exception of one pilot trial,[1] no

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.09.011.

* Corresponding author at: Intensive Care Unit, Wellington Regional Hospital, Capital and Coast District Health Board, Private Bag 7902, Wellington, New Zealand.
E-mail address: paul.young@ccdhb.org.nz (P. Young).

http://dx.doi.org/10.1016/j.resuscitation.2014.09.011
0300-9572/

previous prospective study of different oxygen regimens following resuscitation from OHCA has been performed. There is a sound scientific basis supporting the hypothesis that avoidance of hyperoxia after resuscitation from OHCA might reduce neurological injury.[2] On the other hand, although exposure to hyperoxia appears to be associated with increased in-hospital mortality in observational studies,[3–5] significant heterogeneity in the results of the existing studies means that there is uncertainty about this association.[6] Furthermore, even if the association proved to be robust, it is possible that arterial hyperoxia is a marker of illness severity rather than a determinant of outcome.[7] For example, the presence of poor peripheral perfusion could potentially lead clinicians to increase the inspired oxygen concentration (FiO_2) on the basis of spuriously low peripheral pulse oximetry (SpO_2) recordings. Moreover, even if hyperoxia were truly harmful, any attempt to reduce oxygen exposure in post-resuscitation management may carry with it the potential risk of exposing patients to hypoxia which is also consistently associated with increased mortality risk.[4,7]

As a result of the current uncertainty, a high quality prospective trial evaluating the effect of titrated oxygen therapy on patient outcomes after OHCA is a research priority.[8] With the eventual objective of conducting such a trial, we undertook a feasibility study to evaluate whether or not an individualised oxygen titration regimen designed to limit exposure to hyperoxia in patients with return of spontaneous circulation (ROSC) after OHCA led to an effective reduction in oxygen exposure compared to standard care without exposing patients to a greater incidence and severity of hypoxia.

2. Methods

2.1. Trial design and setting

We performed a prospective, multi-centre, single-blind, parallel-groups, feasibility and safety randomised controlled trial (RCT) comparing titrated oxygen administration to standard care with high concentration oxygen in adults resuscitated from OHCA. This trial was conducted in New Zealand. We intended to enrol patients in Auckland, Christchurch, the Hutt Valley, and Wellington. However, at the time the trial was terminated, site initiation had not been completed in Auckland or Christchurch and, as a result, no participants enrolled were from these centres.

2.2. Participants

Patients who were ventilated *via* a laryngeal mask airway or endotracheal tube were potentially eligible for study inclusion if they had an estimated age of 16–90 years and had ROSC following an OHCA due to a suspected primary cardiac cause with an initial rhythm of VF or VT. Patients were excluded if they were obviously pregnant, living in supported care or a nursing home, were known to have a terminal disease, or if more than 20 min had elapsed since ROSC.

2.3. Randomisation

Eligible patients were randomly assigned to either 'titrated oxygen' or 'standard care' in a 1:1 ratio. Randomisation was achieved by sequential numbered sealed envelopes prepared by a third party who received a randomisation schedule generated by a statistician. There was block randomisation with a block size of six, stratified by Intensive Care Unit (ICU) randomisation centre. For participants in Wellington and the Hutt Valley, randomisation was performed by the attending paramedic who phoned a charge nurse at the Wellington ICU randomisation centre. The ICU charge nurse then opened the next opaque envelope in the numerical sequence and provided the treatment allocation to the paramedic. Where the 'first responder' to the cardiac arrest was the Fire Service,[9] paramedics were still able to randomise patients provided that randomisation could be achieved within 20 min of ROSC.

2.4. Interventions

In patients assigned to titrated oxygen therapy, the prescribed goal was to achieve an SpO_2 of 90–94%. In the pre-hospital period patients were ventilated using a self-inflating resuscitation bag and titration of oxygen delivery was achieved by adjusting the flow of oxygen.[10] Once patients arrived in hospital, the FiO_2 on the ventilator was adjusted as required. In the event that, in the judgement of the attending paramedic, reliable pulse oximetry recordings were not possible in the pre-hospital period, the protocol initially specified that oxygen should be delivered at 1 litre per minute which corresponds to an FiO_2 of approximately 0.40.[10] After enrolment of six patients, the study protocol was amended because of a reported adverse event where a patient assigned to the titrated oxygen group had an unrecognised tension pneumothorax in the pre-hospital period and reliable pulse oximetry recordings could not be obtained. After this amendment, to avoid any risk of severe undetected hypoxia, if pulse oximetry could not be established or stopped working in the pre-hospital period, paramedics were instructed to give the highest FiO_2 possible until such time as working pulse oximetry could be established. Throughout the study, once patients arrived in the hospital, oxygen was titrated according to arterial blood gases if pulse oximetry was believed to be unreliable. In these circumstances, the oxygen delivery was titrated to the arterial oxygen saturation (SaO_2) rather than the partial pressure of oxygen (PaO_2). We chose a target SpO_2 of 90–94% in the titrated oxygen group in order to achieve the greatest separation in SpO_2 levels possible compared to standard care without exposing patients to significant hypoxaemia.

In the pre-hospital period, patients assigned to standard care received oxygen delivered into the self-inflating bag at the highest flow possible. In the emergency department and the ICU the treating clinician determined the oxygen target for the standard care group but a target $SpO_2 > 95\%$ was suggested.

If a patient had a further cardiac arrest after initial ROSC, high concentration oxygen was administered irrespective of which group the patient was assigned to. In these circumstances, if the patient was successfully resuscitated, oxygen was again administered according to the treatment strategy to which the patient had been assigned.

The duration of study treatment was from the time of randomisation until 72 h later or until extubation (whichever was sooner). Patients were blinded as to the treatment allocation; however, due to the nature of the intervention, blinding of investigators was not possible. Apart from the randomised oxygen interventions, patients received standard post resuscitation care which routinely included therapeutic hypothermia.

2.5. Outcomes

The primary end point was the median SpO_2 in the pre-hospital period. Pre-hospital SpO_2 data (maximum one value per minute) were those recorded along with other variables for clinical purposes.

Secondary end points included a range of assessments of oxygen exposure in the emergency department and the ICU. These were the SpO_2 on arrival and every 30 min thereafter while in the emergency department, the SpO_2 and PaO_2 recorded every 6 h up until extubation or 72 h in the ICU, and the number of patients with hypoxia episodes ($SpO_2 < 88\%$) in the ICU. In addition to the oxygenation-related study end points, we measured the arterial partial pressure