Author’s response to reviews

Title: Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: Post ROSC OXYgenation Study

Authors:
Matt Thomas (mjcthom@gmail.com)
Sarah Voss (Sarah.Voss@uwe.ac.uk)
Jonathan Benger (Jonathan.Benger@uwe.ac.uk)
Kim Kirby (Kim.Kirby@swast.nhs.uk)
Jerry Nolan (jerrynolan@me.com)

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Author’s response to reviews:

Dear Editor,

Thank you for the comprehensive reviews of our manuscript, and the opportunity to resubmit.

We have made substantial changes in response to the suggestions of reviewers including the addition of three tables showing more detailed results.

We have expanded the discussion to encompass some newer literature and consideration of key papers.

Below is a point-by-point response to the reviewers with our text in italics.

I have submitted the manuscript with the extensive tracked changes as supplementary material.

Yours sincerely,

Matthew Thomas and co-authors
Clifton W Callaway (Reviewer 1): This trial tested the feasibility of titrating oxygen level during the first hour after cardiac arrest, in preparation for a clinical trial that would test whether such titration is superior to current usual care with high oxygen concentrations. It appears that this intervention can be delivered, but the presentation will benefit from adding a number of important details.

The Introduction makes clear that the trial is intended to test feasibility. Near the end, consider stating exactly what criteria for feasibility are being tested. For example, the trial tests whether, in a majority of patients, paramedics could monitor SpO2, and whether paramedics could titrate FiO2.

Response: Thank you. The manuscript now reads: “In most emergency medical services (EMS) systems, the first hour following ROSC will be prehospital. We therefore designed a trial to examine the feasibility of administering titrated oxygen versus 100% oxygen for the first hour following ROSC to see if paramedics are able to safely titrate oxygen and measure corresponding oxygen saturations.” Full feasibility outcomes are listed in the ”Outcomes” section.

The intervention is depicted in Figure 1. Add how often do paramedics are instructed to titrate oxygen (e.g. every 2 minutes? Every 5 minutes?).

Response: The paramedics were instructed to titrate the oxygen every two minutes – this information has been added to the manuscript. In paragraph 2 of section 3.3 Treatment Protocol

Another aspect of care related to this intervention is the choice of airway. Are all patients endotracheally intubated or do some have supraglottic airways? Are the criteria or protocols different for these different airways?

Response: During this trial patients had their airway managed with either simple airway adjuncts, a supraglottic airway device or tracheal tube. Table 3 now describes the airway used at key time points in the patient’s care (see also Section 4.3).

Group assignment is not perfectly clear. In the methods, the trial seems to be a one-arm trial in which the protocol was intended for all 35 patients attended by a study paramedic. However, the results compare two groups of 17 and 18, and the consort diagram indicates allocation to two interventions.
- Describe the two interventions (only one is described in the methods)
- Describe randomization procedures

Response: The group assignment has now been clarified – the interventions and randomisation processes are described in more detail on page 4 in a new section entitled randomization.

Results section 4.4 describes the successful measurement of SpO2. It would be informative to report what those numbers are. Perhaps a table could describe the time-line of the SpO2 readings at each milestone in the care. How many subjects at each time point had SpO2 >98% or <94%? Were there any episodes of dangerous hypoxemia? These numbers will determine whether treatment is really different.

Response: We have added further information on the measured oxygen saturations in Table 4, and commented on these in the Results and Discussion sections.

Also in section 4.4, the intervention delivery success is not reported. What were the actual flow rates for O2 that were delivered? How many subjects had <10 lpm flow in the titrated group? This is critical to determine if the intervention will actually result in separation of groups, or if all subjects wind up with similar oxygen exposure.

Response: We have added this information, where available, in the text and in Table 6. We have also commented on difficulties in achieving separation in the Discussion section.

Going forward, automated measurement of oxygen exposure or SpO2 levels will increase data fidelity and reliability. Capturing traces or measurements from patient monitors should be a priority for a larger trial.

Response: Thank you, we agree with this. When this pragmatic trial was completed automated measurements of oxygen saturations were not usual practice. If this trial was repeated now those measurements would be available routinely.
Glenn M Eastwood (Reviewer 2): Dear Authors,

The reviewed manuscript reports your study undertaken to evaluate the feasibility of titrating oxygen therapy to OHCA patients by EMS service officers. The endeavour to understand the feasibility of this intervention is of interest and has been explored, as described, by other investigators located outside of the United Kingdom.

As presented I did not find it easy to understand what the 'cluster' referred to. Initially I thought it was going to related to the titration of patients to the '100% oxygen' arm and then switch cluster to the 'titrated oxygen' approach. Yet it appears to read that you have recruited paramedics, provided training and then they were notified of the treatment allocation. Figure 1 only identifies the 'Algorithm for titration of oxygen + the consort diagram is the patient flow diagram. I do not see a cluster figure. Furthermore, aside from the treatment algorithm were there any other study tools or oxygen therapy allocation reminders provided for use at scene?

Response: we have clarified what the clusters are (the paramedic is the cluster), and we have described this in more detail. This is described in the first paragraph of the randomization section on page 4

Background - The shortness of the background together with a clear objective is appreciated. However, as your trial was evaluating the pre-hospital delivery of oxygen to OHCA patients please provide a comment on the rationale/literature to this area.

Response: We have provided more background to the topic and developed the rationale for the study. The expanded background is available on page 3

It may also help that, apart from your 'objective', which I'd recommend calling an 'Aim' is to then comment on the 'objectives of the trial'. By this I mean explaining what you go on to record in relation to feasibility, delivery, recruitment, treatment allocation and separation and patient outcomes. Note, the reference made at the end of the third paragraph doesn't meet the journal requirements.

Response: The objectives have been described in more detail and the section on page 3 has been adjusted to read aim. The reference has been changed

No quality of life data at 90 days was presented, only survival status. Please amend.
Response: We have added this to table 2, which provides further information on 90 day follow-up. We have not recorded the results of the quality of life questionnaires, but whether the questionnaires were returned in order to indicate feasibility.

The Discussion section was shorter than expected.

Response: This has been developed significantly, especially the limitations which encompass reviewers comments.

In the Summary of Findings - please identified 3-4 key findings based on the feasibility or not of your trial. There is the paramedic arm (recruitment, education, delivery), the ability to randomised, the ability to remain in the allocated treatment, and the patient outcomes (delivery of therapy, ability to obtain a useable trace) and arrival to hospital + hospital outcomes. Further, there is only mention of the NZ study and not discuss of this study and its findings in relation to your trial. I would expect a paragraph or more comparing the two studies.

Response: This has been expanded and the two studies compared.

Limitations

While I agree that no separation via ABG findings were identified this was not an aim of your study. The feasiblity aspect looked at the ability to recruit paramedics, the ability of the paramedics to enrol patients, the ability to delivery the treatment, the reasons why treatment was both delivered or abandoned, the ability to record data, the ability to maintain a safe saturation and the ability or not for the hospital to continue treatment allocation. You haven't shown the oxygen saturation data at this stage.

Response: Regrettably, we were unable to record continuous oxygen saturation data in this study. Our partner ambulance service now has automated recording of all observations, so future trials would allow this.

For pragmatic and safety reasons it wouldn't be expected that blinding of treatment allocation in this study at this stage of development (feasibility + safety) would be a limitation. Also, the cluster component still confuses me as I don't understand clearly where the cluster is. The reference to the EXACT study could be address and expanded on in the Future trials section.
Response: See our previous response. The EXACT feasibility trial is now referenced with an expanded commentary on page 9 bottom paragraph.

Your conclusion that it is feasible to enrol paramedics and delivery titrated oxygen therapy in the pre-hospital setting for OHCA patients isn't strongly supported by the data. It would be advisable that, following the known limitations and aspects identified during the PROXY trial that additional feasibility trials be conducted.

Response: Thank you. We have added this proposal, based on your recommendations on page 10.

Comments related to the Manuscript, Tables and Figures

Manuscript -

It was submitted in tracked changed format. Please avoid this.

Figures -

Figure 1 has a 'comment' visible as this too is in tracked-change mode.

Figure 2 is unclear and wording is omitted from several boxes (e.g. allocation box and follow-up box).

Table

Table 1 - I found the working 'Arm A' and 'Arm B' lacked necessary information, please identify the group they represent.

Response: We have addressed these comments, and identified the two arms as requested.

Further more this Table will need the abbreviations explained and would benefit from greater description of the cardiac arrest characteristics. Such characteristics would include greater baseline detail particular in the initial cardiac rhythm (shockable, non-shockable, undetermined), cause of cardiac arrest (medical, traumatic, drowning, drug overdose, electrocution, asphyxia, not identified or missing), witness of cardiac arrest (none, paramedic, bystander, not identified, missing), CPR performed (by bystander, by paramedic, not identified, missing).

Response: We have added more detail to Table 1.
Table 2. Treatment group allocation should be identified here too please. If discharge means 'hospital' please state 'hospital discharge'.

consider a table reporting the characteristics of paramedics is suboptimal. Please consider adding years of service, familiar with equipment, any estimate of the number of CA attended, any educational sessions attended in relation to the study protocol.

Response: We have added data, where available, but regrettably we did not collect some of the data items suggested.

Patrick Sulzgruber (Reviewer 3): Within this manuscript Thomas and coworkers aimed to determine the feasibility of completing a cluster-randomised clinical trial to determine if titrated oxygen therapy for 1 hour after ROSC improves outcome compared with use of 100% oxygen in a paramedic based setting. The scientific question is interesting. However, there are major concerns with respect to the design of the study and presentation of results that need to be considered.

MAJOR COMMENTS

Comment 1: The "Methods" section of the manuscript needs to be described in a more detailed and structured way.

Response: The methods section has been altered substantially to improve the detail and structure on page 4

Comment 2: The manuscript lacks information about the local emergency medical service including whether it is solely paramedic based or covering pre-hospital physicians.

Response: This has been added, section 3.2 on page 4

Comment 3: How were paramedics screened for eligibility? Were there any inclusion or exclusion criteria, or just an unselected sample of volunteers? If so, this might be an selection bias of the present analysis. I recommend to include those information in both "Methods" and "Discussion" section, since I feel it is crucial for both a proper interpretation of the results and reproducibility of the trial.
Response: We have added this information in section 3.2 on page 4 and it is discussed in the discussion under limitations on page 10

Comment 4: Do the authors have any explanation why only 29% of all available paramedics agreed to participate? I am curious whether the obtained subgroup of paramedics is representative for a general "paramedic" population.

Response: We have indicated that this was due to us not pursuing a more active strategy of recruitment, since we needed only a few paramedics for this feasibility study. This is also discussed on page 10 of the discussion section

Comment 5: Since a reliable saturation trace (as the key data) was obtained in only 22/35(69%), I am unsure how the authors could complete data collection in 33 patients. How was the oxygen saturation assessed in those remaining 11 individuals? This needs to be clarified.

Response: The remaining 11 individuals defaulted to 100% oxygen. This has been added to the manuscript and is described on page 5

Comment 6: The authors need to describe how primary outcome data was assessed. How was data on 90d survival obtained? Contacting the patient or hospital?

Response: 90 day survival was collected by contacting the patient by post and sending a QoL questionnaire, which was also returned by post. This has been added to the methods section on page 6.

Comment 7: I am unsure whether the presented data indicate that amongst UK paramedics is feasible to perform a trial of titrated oxygen in the first hour following ROSC after OHCA. On the one hand only 29% of all paramedic were willing to participate in the trial, on the other hand the intervention was initiated in 77% and continued for the full 60 minutes in only in 16 cases. Those issues need to be addressed within the "Discussion" section in a critical fashion.

Response: This has been noted and addressed more critically in the Discussion section. We used a design that was cluster-randomised design by paramedic, which meant that the individuals delivering the intervention and reporting some of the outcomes were not blinded. Paramedics were not selected but volunteered which may mean that our results are not generalizable to all paramedics. Poor recruitment of volunteer paramedics remains an issue for future trials. In our
opinion, individual patient randomisation and paramedic blinding are not practical within UK EMS systems.

Comment 8: Percentages need to be presented within the provided tables.
Response: Percentages have been added

MINOR COMMENTS

Comment 9: I recommend to submit "Figure 1" as a supplementary file.
Response: Figure 1 has been submitted separately.

Comment 10: Page 1, Line 38: Please clarify the reference.
Comment 11: The authors state "During the study period 624 (38%) patients received a resuscitation attempt." It is unclear on what the percentage refers to.
Response: This now reads: “Study paramedics enrolled patients over 6 months. During this time 1,633 OHCAs were identified from ambulance service data, with 624 (38%) undergoing an active resuscitation attempt (Figure 2). A study paramedic was in attendance at 73 (12%) of these active resuscitations”.

Markus B Skrifvars (Reviewer 4): REGARDING the manuscript "Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: Post ROSC OXYgenation Study" submitted to BMC Emergency Medicine.

This manuscript presents a feasibility study for conducting a large RCT on the use of oxygen in cardiac arrest. Given challenges in conducting pre-hospital cardiac arrest research a pilot such as this is warranted.

I have the following comments:
The authors state in the Conclusions "We have shown that it is feasible to complete a randomised trial of titrated versus unrestricted oxygen in the first hour after ROSC following OHCA in the UK". If the authors state this as the main conclusion then they need to make a case for how big this RCT would be, and given the Results of this pilot, how long would that future RCT take to complete? This should also take into account the quite high rate of patients who were randomized but who did not receive the intervention. This would be a major challenge for such a trial.

Response: We have rewritten the relevant sections and been more cautious with the study’s conclusions. We have added on page 10 in sections on limitations of the trial and future trials

- The fact that we do not really know how the intervention succeeded (oxygen saturation, used FiO2) in the lower group is a big problem. Was there any separation between groups?

Response: We have revised the manuscript to address this issue more clearly. The saturations are described in table 4 and blood gases described in paragraph 1 on page 8

- In the previous pilot from New Zealand (Hot or Not) hypoxia was a problem in the lower oxygen group, this is a worry. Where there cases of hypoxia in the titrated arm? How about cases where the patient has aspirated and requires 100% FiO2, where there such cases included?

Response: This information has been added to the manuscript. This is in table 4

- Is 100% FiO2 during transport to hospital current practice in the UK? If not, one may ask whether the 100% FiO2 group receives current standard care or something else. Or are the authors suggesting that indeed patients should receive 100% FiO2?

Response: At the time of the study it was routine practice for cardiac arrest patients to receive 100% oxygen following ROSC and during transport to hospital.

- In both groups 15-25% of the patients did not receive the intervention. Again this is a big concern and should be discussed.

Response: The reasons for this have been added, and are discussed in more detail in the revised manuscript.
- Given the small sample size I am not convinced that Table 2 is needed.

Response: Other reviewers have requested changes to this table, so we have retained it currently. We have expanded information available in figure 2 also.

- The authors cite the smaller study in AMI patients suggesting that oxygen administration may be harmful. There is however a larger study from Sweden that showed no difference in outcome between those who received oxygen and those who did not. There was no benefit but no harm either.

Response: We note the Swedish study, however this reference has been retained to highlight that hyperoxia is potentially harmful.

- What the optimal oxygen level is in OHCA patients is currently unclear. Some studies suggest harm and some do not. I miss a more nuanced discussion of this in the paper.

Response: We have added some discussion of this, however as a feasibility study our primary aim was to report our stated outcomes. We hope other papers will debate the potential benefits and harms of hyperoxia. We have expanded the discussion section on page 10 to include this information.

- The authors cite the paper by Kuisma. This is an important paper but it needs to be stated that in that paper there was a difference in NSE favoring the lower FiO2 group in one subgroup only (those who did not receive TTM).

Response: We have updated the Background section accordingly. page 3 paragraph 3

All in all the authors have studied a new approach to perform an RCT in the prehospital setting. They have some valuable data but I think the presentation and analysis can be improved.

Response: Thank you; the paper has been amended substantially.

Janet Bray (Reviewer 5): This study examined the feasibility of running an oxygen titration RCT post-OHCA in the prehospital environment. There are some details, results and discussion
missing from the manuscript. Of note the EXACT pilot study has been published in Resuscitation but is not cited or discussed in the manuscript. The paper also does not provide much information about the safety of the intervention. Other issues are:

1) There are a few typos in background.

Response: These have been corrected.

2) Full patient inclusion and exclusion criteria are not described.

Response: These are described here below - as you can see the full criteria are long and add considerably to the word count of the paper, we consider the brevity and focus of the paper benefits the shorter version. If requested we can add this detail or provide as a supplement. Paramedics were the cluster used to randomise.

Inclusion criteria
A patient may be enrolled in the study if ALL of the following apply:

1. They have sustained a cardiac arrest in the pre-hospital setting believed to be of a nontraumatic cause. Cardiac arrest will be defined according to the Utstein Definition as "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. If an EMS provider or physician did not witness the cardiac arrest, he/she may be uncertain as to whether a cardiac arrest actually occurred." For the purposes of this study, patients will be eligible for inclusion if they are attended by ambulance staff and are believed by those staff to have suffered a cardiac arrest.

2. ROSC (indicated by signs of circulation: usually a palpable central or peripheral pulse) for greater than 2 minutes (sustained ROSC) has been achieved

3. Attended by a paramedic participating in the trial

4. Known, or believed to be, 18 years of age, or older

5. The participating paramedic intends to transport the patient to one of the three designated receiving hospitals: Bristol Royal Infirmary, Southmead or Royal United Hospital, Bath.

Exclusion criteria
A patient may not be enrolled in the study if ANY of the following apply
1. Less than 18 years old

2. Cardiac arrest believed to have been caused by trauma (including hanging and drowning)

3. Entered into the study previously

4. Detained by Her Majesty's Prison Service

3) The timing of first titration is not described, or how long paramedics were instructed to wait before next level of titration.

Response: See above. This information has now been added on page 5 section 3.3 paragraph 2

4) What happened if patients became hypoxic? What level of oxygenation was acceptable?

Response: We have clarified this in the paper: the lower limit of the target saturation range was 94%, and patients were given 100% oxygen if they were at risk of hypoxia. Section 3.3 paragraph 2 page 5

5) What is SWASFT?

Response: This refers to our partner ambulance service, however we have removed this abbreviation for clarity.

6) How were paramedics randomised?

Response: Additional information relating to the randomisation process has been added. A new section entitled randomisation is added on page 4

7) Why was paramedic participation so low? This requires discussion and implications for feasibility.

Response: See our previous response; we have also modified the Discussion section accordingly. pg 10 section 5.2 limits of the trial
8) What were the criteria for exclusion in 37 patients?

Response: This is due in the majority of cases to the cardiac arrest being caused by trauma.

9) Shouldn't Figure 2 feature rates of ROSC in rather than resuscitated in excluded box? Why did you included cases not seen by PROXY paramedics -how were these cases "assessed for eligibility" as per box above? And both groups are down as "allocated to intervention".

Response: This has been revised. We recorded all cardiac arrests in the recruiting region during the study period.

10) It is unclear why 8 patients didn't receive allocated intervention?

Response: An explanation has been added.

11) Figure 2 - end of text in follow-up box is hidden -just says "poor"

Response: This has been corrected.

12) Tables 1 and 2 groups are labelled arm a and arm b -not clear which group is which?

Response: The identity of the two arms is now stated.

13) Table 1 -needs to have n(%).

Response: Percentages have been added to Table 1.

14) Table 1 -do you have information on rhythm, aetiology, downtime, oxygen saturation, airway type?

Response: We have included all the additional information that is available including initial rhythm. We have added airway type as an additional table-table 3 and oxygen saturation as table 4. We did record downtime but have found it an unreliable so have not described it in this manuscript.
15) What level of oxygen titration was achieved?
Response: We have added this to the paper and included a commentary in the discussion section. This is included as table 5.

16) Why don't the outcomes match those on the trial registration site?
Response: This trial was originally intended to be prospectively registered, however this was overlooked due to an administrative error. The same information was used to retrospectively register it. The outcome measures in the paper are those approved by the ethics committee.

17) Table 1. There are large differences between groups that are not mentioned.
Response: We have added a consideration of this issue to the manuscript although as a feasibility trial we have not emphasised differences as they are likely to be chance.

18) Table 2. There are large differences in survival between the two groups even with this small sample size. This requires discussion and implications for main study.
Response: In our view this feasibility study is too small to permit any inferences about the possible treatment effect of titrated oxygen, and the differences observed are likely to be due to chance alone.

19) What were the rates of re-arrest in each arm?
Response: This has been added to table 1.

20) There is virtually no discussion. What were the differences between your study, the Young and Bray studies?
Response: We have revised and expanded the Discussion section considerably in response to this and other comments on page 9 and 10.

21) Please elaborate on methods of measuring tissue and brain oxygen in discussion.
Response: A reference has been added, however we have de-emphasised the importance of this in favour of accurate recording of peripheral oxygen saturations.