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Clinical paper

Conservative or liberal oxygen therapy in adults after cardiac arrest
An individual-level patient data meta-analysis of randomised controlled trials

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Abstract

Aim: The effect of conservative versus liberal oxygen therapy on mortality rates in post cardiac arrest patients is uncertain.

Methods: We undertook an individual patient data meta-analysis of patients randomised in clinical trials to conservative or liberal oxygen therapy after a cardiac arrest. The primary end point was mortality at last follow-up.

Results: Individual level patient data were obtained from seven randomised clinical trials with a total of 429 trial participants included. Four trials enrolled patients in the pre-hospital period. Of these, two provided protocol-directed oxygen therapy for 60 min, one provided it until the patient was handed over to the emergency department staff, and one provided it for a total of 72 h or until the patient was extubated. Three trials enrolled patients after intensive

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https://doi.org/10.1016/j.resuscitation.2020.09.036
Received 30 August 2020; Accepted 30 September 2020
Available online xxx

Please cite this article in press as: P.J. Young, M. Bailey, R. Bellomo et al. Conservative or liberal oxygen therapy in adults after cardiac arrest. Resuscitation (2020), https://doi.org/10.1016/j.resuscitation.2020.09.036

care unit (ICU) admission and generally continued protocolised oxygen therapy for a longer period, often until ICU discharge. A total of 90 of 221 patients (40.7%) assigned to conservative oxygen therapy and 103 of 206 patients (50%) assigned to liberal oxygen therapy had died by this last point of follow-up; absolute difference; odds ratio (OR) adjusted for study only; 0.67; 95% CI 0.45 to 0.99; P = 0.045; adjusted OR, 0.58; 95% CI 0.35 to 0.96; P = 0.04.

Conclusion: Conservative oxygen therapy was associated with a statistically significant reduction in mortality at last follow-up compared to liberal oxygen therapy but the certainty of available evidence was low or very low due to bias, imprecision, and indirectness.

PROSPERO registration number: CRD42019138931.

Keywords: Oxygen therapy, Cardiac arrest, Hypoxic ischaemic encephalopathy, Hyperoxaemia, Hypoxaemia, Randomised controlled trial, Individual patient data meta-analysis

Introduction

Withdrawal of life sustaining treatment based on prognostication of a poor neurological outcome following hypoxic ischaemic brain injury is a common cause of death among post cardiac arrest patients on the Intensive Care Unit (ICU).[1] It is biologically plausible that the liberal use of oxygen that occurs with standard management of comatose post cardiac arrest patients contributes to secondary brain injury.[2] In particular, exposure to hyperoxaemia worsens brain damage in animal models of hypoxic ischaemic encephalopathy.[3] Hyperoxaemia is independently associated with increased mortality risk in some observational studies of post cardiac arrest patients.[4–7] However, this association has not been shown in all studies[8,9] and conservative use of oxygen may increase hypoxaemia, which is consistently associated with increased mortality risk.[4–9] Thus, clinicians are uncertain about the optimal oxygen target in these patients.

Several randomised controlled trials have compared conservative with liberal oxygen therapy in patients resuscitated from cardiac arrest.[10–14] Some other trials have compared such oxygen therapy regimens in heterogeneous ICU patient populations[15–17] and these trials include patients with possible hypoxic ischaemic encephalopathy. However, no individual patient level data meta-analysis that includes all patients with possible hypoxic ischaemic encephalopathy from randomised controlled trials of conservative vs. liberal oxygen has been performed.

We performed a systematic review, aggregate data meta-analysis and individual level patient data meta-analysis using data from patients post cardiac arrest with possible hypoxic ischaemic encephalopathy from randomised controlled trials that compared liberal versus conservative oxygen regimens. Our primary hypothesis was that conservative oxygen therapy would reduce all-cause mortality at the last point of follow-up. Our secondary hypothesis was that conservative oxygen therapy would increase the proportion of patients with a favourable functional outcome at last point of follow-up.

Methods

Study design, trial and patient-level eligibility criteria

We performed a systematic review, aggregate data meta-analysis and individual patient data meta-analysis of randomised controlled trials. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from inception to August 11, 2020, without language restrictions, for randomised controlled trials comparing the use of liberal and conservation oxygen therapies in adults with suspected hypoxic ischaemic encephalopathy. The specific search strategies used are shown in the eMethods in the Electronic Supplemental material (ESM). Randomised controlled trials that included heterogeneous populations of patients who were mechanically ventilated in ICU were included provided that individuals who fulfilled our patient level eligibility criteria could be identified using baseline characteristics in respective study databases.

We included adults (aged at least 18 years of age) with possible hypoxic ischaemic encephalopathy, defined as: (i) mechanically ventilated in ICU with an ICU admission diagnosis of cardiac arrest, OR (ii) a clinical ICU admission diagnosis of confirmed or suspected hypoxic ischaemic encephalopathy, OR (iii) unconscious (GCS $<$ 9) with an endotracheal tube or supraglottic airway in situ with sustained return of spontaneous circulation (ROSC) following a cardiac arrest. We excluded patients who were pregnant.

This trial was prospectively registered (PROSPERO registration number: CRD42019138931). All trials included in this analysis received ethics approval and additional approvals to allow for data sharing were obtained where required.

Data extraction plan

Titles and/or abstracts of studies were retrieved using the search strategy and those from additional sources were screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of potentially eligible studies were retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of a particular study was resolved through discussion with a third reviewer.

Risk of bias (quality assessment)

Data supplied for included randomised controlled trials were checked for: missing data; internal data consistency; randomisation integrity (balance of patient characteristics at randomisation, pattern of randomisation); follow-up and censoring pattern. Summary tables were checked with the trial protocol and latest trial report or publication. Any discrepancies or unusual patterns were checked with the study investigator.

Outcome variables

The main outcomes were pre-specified in advance and were as follows: (i) mortality at last reported time point (primary end point); (ii) "good" functional outcome defined at last reported time point based on either: a cerebral performance category (CPC) score of 1 or 2, OR a Glasgow Outcome Scale - Extended (GOS-E) score of 5 or more; (iii) survival time; (iv) in-hospital mortality; (v) 30 day mortality; (vi) 90 day mortality; and, (v) 180 day mortality.

Definitions of intervention and control groups

The treatment arm with the lower oxygen target, measured by any one of the following: fraction of inspired oxygen (FIO_2), arterial partial pressure of oxygen (PaO_2), arterial oxygen saturation (measured by blood analysis), or peripheral oxygen saturation (measured by a pulse oximeter [SpO_2]) was defined as the conservative arm (intervention).

The treatment arm with the higher oxygen target, measured by any one of the following: fraction of inspired oxygen (FIO_2), arterial partial pressure of oxygen (PaO_2), arterial oxygen saturation (measured by blood analysis), or peripheral oxygen saturation (measured by a pulse oximeter [SpO_2]) was defined as the liberal arm (comparator/control).

Baseline variables of interest, effect modifiers, and confounders

Investigators for the included studies supplied line by line individual participant data comprising: (i) de-identified patient study number; (ii) treatment group assignment; (iii) baseline characteristics: age; gender; arrest location; bystander response; first monitored rhythm; cause of arrest; presence of ST-elevation myocardial infarction (STEMI); time to response; time to defibrillation; time to sustained ROSC; comorbidities; drugs given during resuscitation; pre-randomisation mean arterial pressure; pre-randomisation arterial partial pressure of carbon dioxide ($PaCO_2$); (iv) co-interventions: use of targeted temperature management; neuroprognostication tests; (v) oxygenation data: all oxygenation data available from all studies; (vi) outcome data: mortality at last reported time point; survival time from randomisation; in-hospital & day 180 mortality; cause-specific mortality (neurological cause of death vs. non-neurological cause of death); neurological outcome at six months following randomisation (based on CPC and/or GOS-E).

Subgroups

Pre-specified subgroup pairs of interest were as follows: (i) patients with in-hospital arrest versus out of hospital arrest; (ii) patients with a medical cause of cardiac arrest versus a non-medical cause of cardiac arrest.

Statistical analysis plan

Aggregate data were initially used for an analysis of all-cause mortality at last follow-up. We recorded numerators and denominators by treatment group from which estimates of risks of death were derived. Data were pooled using the Mantel-Haenszel weighting method and presented as relative risk (RR) and 95% confidence intervals (CI). All further analyses were conducted using individual level patient data from all randomised participants. Baseline comparisons by treatment group were performed using a X^2 test for proportions or a Fisher's Exact test where numbers were small, Student's T-test for normally distributed data and Wilcoxon Rank sum test otherwise with results reported as numbers (%), mean SD, or median [IQR] respectively.

Outcomes were analysed on an intention to treat basis with no imputation unless specified. Mortality and the proportion of patients with a good neurological outcome by treatment group were compared using logistic regression adjusting for study as a fixed effect. The numbers at risk in each group and the number and proportion of events were reported as well as the equivalent absolute risk difference and relative risk along with corresponding 95% confidence intervals (95% CI). The proportion of patients with a good neurological outcome by treatment group were analysed and reported in a similar fashion.

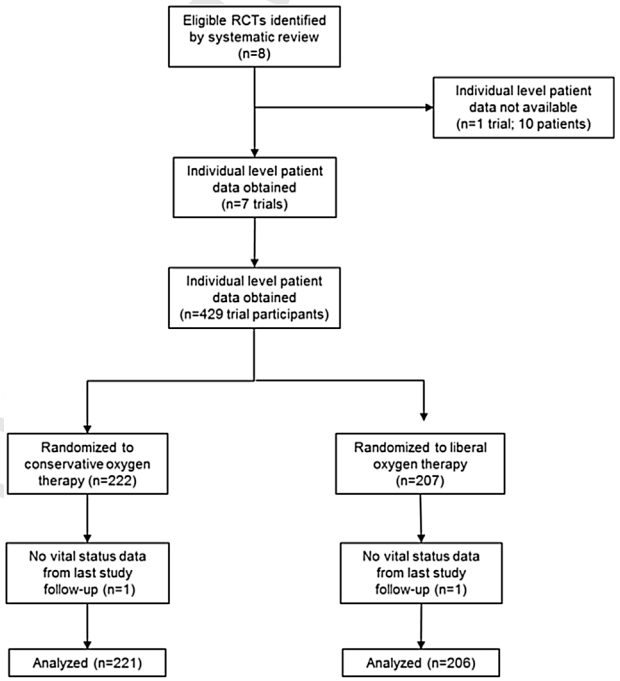

Fig. 1 – Participant flow diagram.
Abbreviations: RCTs: randomised controlled trials.

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Survival times were compared using Cox-proportional hazards regression adjusted for study as a fixed effect. Results were presented using Kaplan–Meier curves with group comparison using a log-rank test. We undertook sensitivity analyses adjusting for pre-specified covariates that predict outcome in cardiac arrest patients (age, whether or not the cardiac arrest was witnessed, whether or not there was bystander CPR, whether there was a shockable rhythm, the time until sustained return of circulation). We conducted an additional sensitivity accounting for an observed baseline imbalance in the proportions of patients by treatment group who had a previous myocardial infarction and who had a cardiac arrest with a medical cause. In addition, for survival we conducted a sensitivity analysis in which all hospital survivors from the EXACT pilot trial were assigned a survival time of 30 days. This assumption was made because survival times for hospital survivors were not available and was based on the findings from PARAMEDIC-2 where hospital mortality in a similar population was found to closely mirror 30 day mortality.[18] In all analyses a two-sided P value of 0.05 was used to indicate statistical significance. P values for secondary end points and subgroup analyses were not adjusted for multiplicity and should be considered hypothesis-generating.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and Review Manager (RevMan) Version 5.4. (The Cochrane Collaboration, 2020)

Results

Data sources

Individual level patient data were obtained from seven out of eight randomised controlled trials identified in our systematic review with a total of 429 trial participants included. Details of the included trials and of the trial from which data could not be obtained are shown in the Table S1 (ESM).

Table 1 – Baseline characteristics.[a]

Characteristic	Conservative oxygen (n = 222)	Liberal oxygen (n = 207)
Age – yr	63.0 ± 14.3	61.1 ± 14.9
Male sex – no. (%)	178 (80.2%)	163 (78.7%)
Arrest location in-hospital – no. (%)	10 (4.5%)	13 (6.3%)
Emergency department	3 (1.4%)	6 (2.9%)
Hospital ward	5 (2.3%)	3 (1.4%)
ICU	1 (0.5%)	0 (0%)
Operating theatre	0 (0%)	1 (0.5%)
Other location in hospital	1 (0.5%)	3 (1.4%)
Arrest location out-of-hospital		
Home/residence	72 (32.4%)	67 (32.4%)
Assisted living/nursing home	1 (0.5%)	2 (1.0%)
Other location (not in hospital)	80 (36.0%)	70 (33.8%)
Arrest location data missing	59 (26.6%)	55 (26.6%)
Witness arrest – no. (%)	193 (86.9%)	172 (83.1%)
Received bystander CPR – no. (%)	172 (77.5%)	155 (74.9%)
First monitored rhythm – no. (%)		
AED shockable/VF/pulseless VT*	184 (82.9%)	154 (74.4%)
Pulseless electrical activity	20 (9.0%)	21 (10.1%)
Asystole	9 (4.1%)	12 (5.8%)
Bradycardia	0 (0%)	3 (1.4%)
AED non-shockable	2 (0.9%)	1 (0.5%)
No cardiac arrest	2 (0.9%)	1 (0.5%)
First monitored rhythm data missing*	5 (2.3%)	14 (6.8%)
Cause of arrest – no. (%)		
Medical*	205 (92.3%)	177 (85.5%)
Asphyxia	3 (1.4%)	4 (1.9%)
Drug overdose	0 (0%)	2 (1.0%)
Drowning	0 (0%)	1 (0.5%)
Trauma	0 (0%)	1 (0.5%)
Cause of arrest data missing	14 (6.3%)	22 (10.6%)
Previous AMI*	18/148 (12.2%)	29/138 (21.0%)
Response times - minutes		
Time to EMS or resuscitation team response	7.3 ± 5.1; n=172	6.6 ± 4.6; n = 171
Time to defibrillation, median [IQR]	6.5 [4–11]; n=82	6 [1–9]; n = 81
Time to ROSC	14.7 ± 10.5; n=172	15.2 ± 12; n = 171

Plus-minus values will be expressed as mean ± SD.
Data on whether or not the arrest was witnessed and whether bystander CPR was performed were missing for four patients allocated to liberal oxygen therapy.
Abbreviations: AED: automated external defibrillator; CPR: cardiopulmonary resuscitation; EMS: emergency medical services; ICU: intensive care unit; ROSC: return of spontaneous circulation; VF: ventricular fibrillation; VT: ventricular tachycardia.
[a] Statistically significant differences in baseline characteristics between groups are indicated by * for $P < 0.05$.

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Table 3 – Outcomes.

	Conservative oxygen (n = 222)	Liberal oxygen (n = 207)	Odds ratio (95% CI); P value	
			Adjusted for study[a]	Adjusted for all specified covariates[b]
Primary outcome – n/N (%)				
Mortality at last follow-up	90/221 (40.7%)	103/206 (50%)	0.67 (0.45–0.99); P = 0.045	0.58 (0.35–0.96); P = 0.04
Secondary outcomes – n/N (%)				
Favourable neurological outcome at six months[c]	85/154 (55.2%)	66/145 (45.5%)	1.53 (0.96–2.46); P = 0.08	1.62 (0.95–2.76); P = 0.07
30-day mortality	81/194 (41.8%)	97/191 (50.8%)	0.63 (0.41–0.97); P = 0.04	0.63 (0.38–1.05); P = 0.08
90-day mortality	72/180 (40.0%)	89/180 (49.4%)	0.67 (0.44–1.03); P = 0.08	0.65 (0.39–1.08); P = 0.10
180-day mortality	65/165 (39.4%)	76/158 (48.1%)	0.69 (0.44–1.08); P = 0.10	0.67 (0.40–1.12); P = 0.13
In-hospital mortality	69/161 (42.9%)	78/148 (52.7%)	0.66 (0.42–1.04); P = 0.08	0.54 (0.29–1.01); P = 0.05

Abbreviation: CI: confidence interval.
[a] Adjusted for study as a fixed effect.
[b] Adjusted for age, whether or not the cardiac arrest was witnessed, whether or not there was bystander CPR, whether there was a shockable rhythm, the time until sustained return of circulation.
[c] This analysis was limited to patients from trials where neurological outcomes were formally assessed at six months.

Patient characteristics

Of the 429 trial participants included in this analysis, 222 were assigned to conservative oxygen therapy and 207 were assigned to liberal oxygen therapy (Fig. 1). Compared with patients assigned to liberal oxygen therapy, those assigned to conservative oxygen therapy were more likely to have an initial rhythm that was shockable, more likely to have medical cause of cardiac arrest, and less likely to have had a prior myocardial infarction (Table 1). In other respects, the study groups had similar baseline characteristics (Table 1 and Table S2, ESM).

Table 2 – Oxygen regimens tested in each study.

Study	Timing of study treatment	Conservative oxygen group	Liberal oxygen group
CLOSE	Within 24 h of initiation of invasive mechanical ventilation in ICU.	A target SpO_2 of 88–92% was applied until the patient was discharged from ICU unless an FIO_2 of >0.8 was required, in which case, SpO_2 targets were at the discretion of the treating clinician	A target SpO_2 of ≥96% was applied until the patient was discharged from ICU
COMACARE	Following ICU admission	A target PaO_2 from 75 mmHg to 112.5 mmHg for 36 h from the ICU admission or until the patient was extubated or ventilation was set to a spontaneous mode, whichever occurred first	A target PaO_2 from 150 mmHg to 187.5 mmHg for 36 h from the ICU admission or until the patient was extubated or ventilation was set to a spontaneous mode, whichever occurred first
EXACT PILOT	Prehospital after sustained ROSC, when an advanced airway was in place, and when the SpO_2 was ≥96%	Initially (Sept 2015–March 2016) patients received 2 l/min; however, after April 2016 initial administration of oxygen was at 4 l/min with a reduction to 2 l/min the SpO2 was ≥90%	Oxygen was delivered at >10 l/min via a bag-valve reservoir until the patient was handed over to the ED staff
HOT OR NOT	Prehospital after sustained ROSC, when an advanced airway was in place	A target SpO_2 of 90–94% was applied for 72 h or until the patient was extubated, whichever was sooner	In the pre-hospital period, the highest FIO_2 possible was used. In hospital, the treating clinician could determine the SpO_2 target but SpO_2>95% was suggested. Protocol-directed oxygen therapy continued for 72 h or until the patient was extubated, whichever was sooner
ICU-ROX	Within two hours of invasive mechanical ventilation in the ICU	The upper limit monitored SpO_2 alarm was set to sound when the level was >96%, and the FIO_2 was decreased to 0.21 if the SpO_2 was ≥90%. An alternative SpO2 limit could be used at the discretion of the treatment. Patients received the assigned oxygen-therapy strategy until discharge from the ICU or 28 days after randomisation, whichever was earlier	The use of an FIO_2 <0.3 in patients who were invasively mechanically ventilated was discouraged. Patients received the assigned oxygen-therapy strategy until discharge from the ICU or 28 days after randomisation, whichever was earlier
KUISMA	Prehospital immediately following ROSC	FIO_2 0.3 for 60 min; increased in 0.1 increments if the SpO_2 was <95% for ≥5 minutes	FIO_2 1.0 for 60 min
PROXY	Prehospital immediately following ROSC	A target SpO_2 of 94–98% was applied for 60 min	FIO_2 1.0 for 60 min

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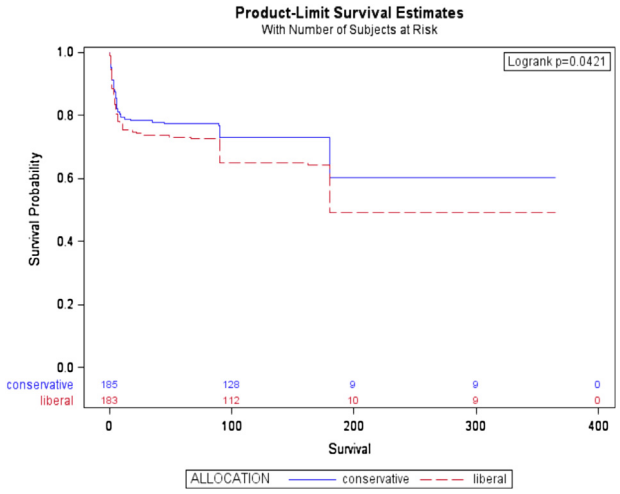

Fig. 2 – Kaplan–Meier survival estimates of the probably of survival*.
***The EXACT pilot trial was excluded from this analysis because duration of survival data were not recorded. The hazard ratio adjusted for study was 0.72 (95%CI, 0.52 to 0.97), P = 0.03. The hazard ratio adjusted for age, whether or not the cardiac arrest was witnessed, whether or not there was bystander CPR, whether there was a shockable rhythm, the time until sustained return of circulation; whether the patient had previously had an acute myocardial infarction, and whether there was a cardiac arrest of presumed cardiac cause, 0.79 (95%CI, 0.56–1.10), P = 0.16.**

Oxygen therapy

Four trials enrolled patients in the pre-hospital period (Table 2). Of these, two provided protocol-directed oxygen therapy for 60 min, one provided it until the patient was handed over to the emergency department staff, and one provided it for a total of 72 h or until the patient was extubated. Three trials enrolled patients following ICU admission. The duration of protocol-directed oxygen therapy was generally longer in these trials than in the trials that commenced study treatment in the pre-hospital period with the largest providing protocol-directed oxygen therapy for up to 28 days.

Co-interventions

Data on co-interventions and neuroprognostic testing were not available for all participants because they were not collected in all trials (Table S3, ESM). However, for those participants where data were available, there were no differences between treatment groups in the use of amiodarone or adrenaline during resuscitation. Targeted temperature management was used in over 90% of patients in both groups. Data on neuroprognostic tests undertaken were only available for one study,[19] but for this study, use of such testing was similar by treatment group.

Patient outcomes

The duration of follow-up varied by study ranging from follow-up to hospital discharge to follow-up to 365 days (Table S1, ESM). A total of 90 of 221 patients (40.7%) assigned to conservative oxygen therapy and 103 of 206 patients (50%) assigned to liberal oxygen therapy had died by this last point of follow-up; odds ratio (OR) (adjusted for study only); 0.67; 95% CI 0.45–0.99; P = 0.045; OR (adjusted for study and pre-specified baseline variables), 0.58; 95% CI 0.35–0.96; P = 0.04 (Table 3 and Fig. 2). Findings were similar in a sensitivity analysis incorporating adjustment for observed baseline imbalances between treatment groups including whether the patient had previously had an acute myocardial infarction and whether the cardiac arrest was of presumed to have a medical cause (Table S4, ESM). Findings in the aggregate data meta-analysis were similar to those of the individual patient data meta-analysis (Fig. 3).

Secondary outcomes

In-hospital, 30-day, 90-day, and 180-day mortality were consistently lower in patients assigned to conservative oxygen therapy (Table 3). Among patients from trials where neurological outcomes were formally assessed at six months, a total of 85 of 154 (55.2%) assigned to conservative oxygen therapy and 66 of 145 (45.5%) assigned to liberal oxygen therapy had a favourable neurological outcome at six months; OR 1.53; 95% CI 0.96–2.46; P = 0.08; adjusted OR 1.62; 95% CI 0.95–2.76; P = 0.07. Findings in relation to all secondary outcome variables were similar in sensitivity analyses incorporating adjustment for observed baseline imbalances between treatment groups in whether the patient had previously had an acute myocardial infarction and whether the cardiac arrest was of presumed to have a medical cause (Table S4, ESM). Survival analyses using imputation for duration of survival among the EXACT pilot trial patients are shown in Figure S1 (ESM).

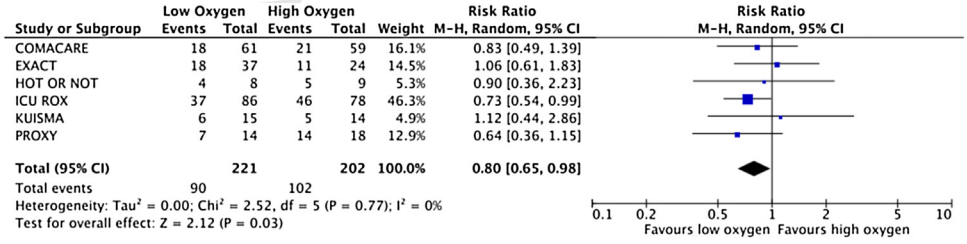

Fig. 3 – Aggregate data meta-analysis findings for the effect of liberal oxygen vs conservative oxygen on mortality at last follow-up*.
***The CLOSE-I trial was not included in the aggregate data meta-analysis because all four patients in the CLOSE-I trial who had a cardiac arrest prior to randomisation we allocated to liberal oxygen.**

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Subgroups

A total of 406 patients had an OHCA and 23 had an IHCA. All but 11 patients had a cardiac arrest of presumed medical cause. There were no statistically significant interactions between treatment group allocation and the various study outcomes for patients by location of arrest (Table S5, ESM). Because of small numbers, interaction analyses were not performed based on whether or not cardiac arrest was of a presumed primary medical cause. Findings limited to patients with a presumed primary medical cause of arrest, which were similar to the findings of the overall analyses, are shown in Table S6 (ESM).

Discussion

In this individual patient data meta-analysis of randomised controlled trials comparing conservative with liberal oxygen therapy in patients with possible hypoxic ischaemic encephalopathy, conservative oxygen was associated with significantly reduced mortality at the last follow-up. These findings were robust to adjustment for pre-specified baseline covariates and in other sensitivity analyses.

Our primary outcome variable findings are consistent with animal data[3] and some observational data[4–7,9] and support the hypothesis that conservative oxygen therapy reduces mortality in cardiac arrest patients. The findings of our aggregate data meta-analysis and individual data meta-analysis are concordant but the latter analysis offers the considerable advantage of allowing adjustment for important patient-level baseline variables that are powerful predictors of outcome in cardiac arrest patients.[20] There was no evidence of heterogeneity in findings of trials included. Our study synthesises individual patient-level data from all trials identified by systematic review with the exception of ten patients admitted to ICU following a cardiac arrest in the Oxygen-ICU trial.[17] Because we used mortality at last known point of contact as our primary outcome variable, most trial participants were included in our primary analysis.

Despite the strengths of our analysis, based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach,[21] we consider that the certainty of evidence supporting conservative oxygen therapy following cardiac arrest is low or very low for a number of reasons. First, some data for secondary outcomes were not available for some patients and the between-group differences in favourable neurological outcomes, and most mortality outcomes were not statistically significant. Secondly, oxygen therapy is, by necessity, an open label therapy and we cannot exclude the possibility that patients assigned to conservative oxygen therapy were treated differently from patients assigned to liberal oxygen therapy. Although mortality has a low risk of ascertainment bias, decisions related to withdrawal of life sustaining therapies could have been influenced by knowledge of treatment assignment and no trials protocolised decision-making in relation to withdrawal of life-sustaining therapies.[22] Thirdly, the 95% confidence intervals around effect size estimates are imprecise and even one additional death in the conservative oxygen therapy group in any trial would mean that the primary end point findings were not statistically significant. Fourthly, the included trials evaluated oxygen regimens in a mixture of pre-hospital and ICU settings. Moreover, oxygen regimens varied in duration from one hour to 28 days or more, and the amount of oxygen delivered in the regimens tested varied. Thus, we consider that the strength of our findings should be downgraded because of indirectness. Finally, further data are needed on the effect of different oxygen regimens on neurological outcomes, in particular. Such data were available for fewer than 70% of patients included in this analysis.

Conclusions

In this individual patient data meta-analysis of randomised controlled trials conservative oxygen therapy was associated with reduced mortality at last follow-up compared with liberal oxygen therapy. However, based on the risk of bias, imprecision of effect size estimates, and indirectness of evidence for any specific approach to oxygen therapy, we consider that the certainty of available evidence supporting the use of conservative oxygen therapy in cardiac arrest patients is low or very low.

Authorship statement

I confirm that all listed authors have made substantial contributions to:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,
(2) drafting the article or revising it critically for important intellectual content,
(3) final approval of the version to be submitted.

Conflict of interest statement

Paul Young is the Chief Investigator for the Mega-ROX trial, which is comparing conservative and liberal oxygen therapy in ICU patients including post cardiac arrest patients. Stephen Bernard is the Chief Investigator for NHMRC funded EXACT trial, which is comparing conservative and liberal oxygen therapy in post cardiac arrest patients. Jerry Nolan is a co-investigator on the PROXY study which was funded by an NIHR Programme Development Grant (RP-DG-0612-10004) and is evaluating oxygen regimens in cardiac arrest patients. Daniel Martin has received lecture and consultancy fees from Siemens Healthineers and Edwards Lifesciences. Markus Skrifvars reports receiving speaker's fees and travel grants from BARD Medical (Ireland). Q5

Acknowledgements

This research was conducted during the tenure of a Health Research Council of New Zealand Clinical Practitioner Fellowship held by Paul Young. Janet Bray is funded by a Heart Foundation of Australia Fellowship.

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.2020.09.036.

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Please cite this article in press as: P.J. Young, M. Bailey, R. Bellomo et al. Conservative or liberal oxygen therapy in adults after cardiac arrest. Resuscitation (2020), https://doi.org/10.1016/j.resuscitation.2020.09.036