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A randomized controlled trial comparing controlled reoxygenation and standard cardiopulmonary bypass in paediatric cardiac surgery

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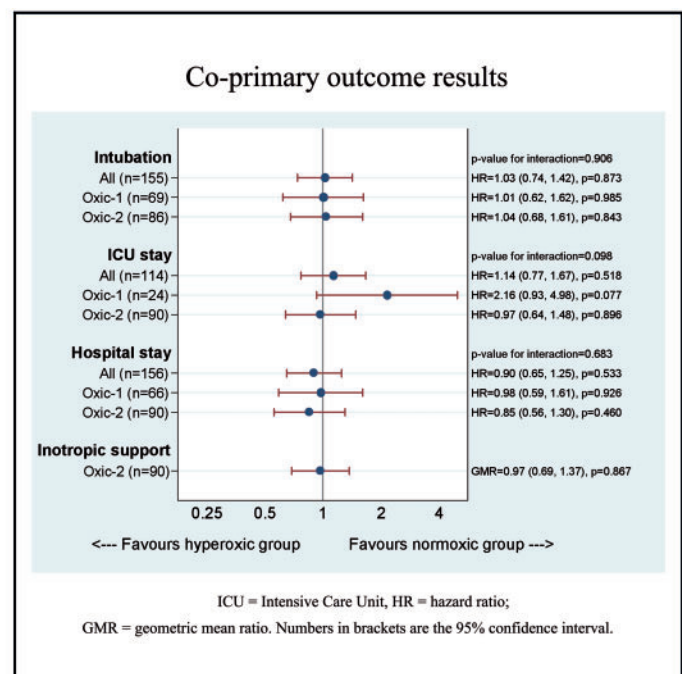
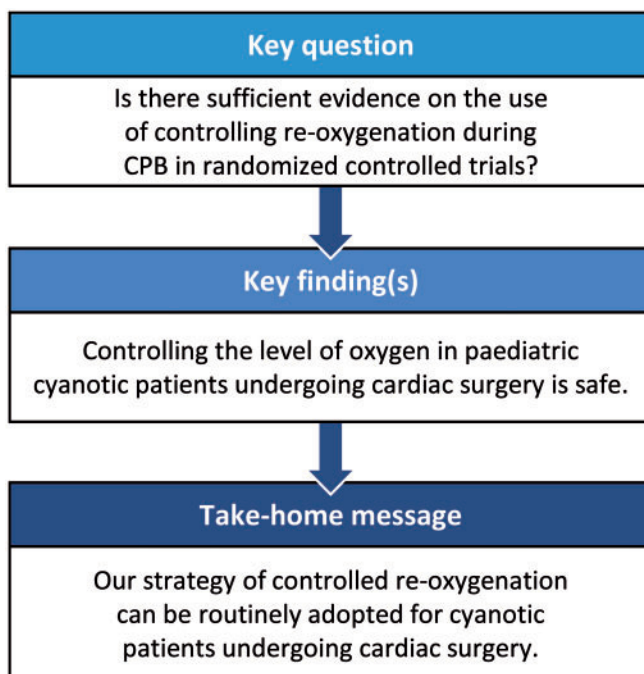
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Abstract

OBJECTIVES: Controlled reoxygenation on starting cardiopulmonary bypass (CPB) rather than hyperoxic CPB may confer clinical advantages during surgery for congenital cyanotic heart disease.

METHODS: A single-centre, randomized controlled trial was carried out to compare the effectiveness of controlled reoxygenation (normoxia) versus hyperoxic CPB in children with congenital cyanotic heart disease undergoing open-heart surgery (Oxic-2). The co-primary clinical outcomes were duration of inotropic support, intubation time and postoperative intensive care unit (ICU) and hospital stay. Analysis of the primary outcomes included data from a previous trial (Oxic-1) conducted to the same protocol.

RESULTS: Ninety participants were recruited to Oxic-2 and 79 were recruited to the previous Oxic-1 trial. There were no significant differences between the groups for any of the co-primary outcomes: inotrope duration geometric mean ratio (normoxia/hyperoxic) 0.97, 95% confidence interval (CI) (0.69–1.37), *P*-value = 0.87; intubation time hazard ratio (HR) 1.03, 95% CI (0.74–1.42), *P*-value = 0.87; postoperative

ICU stay HR 1.14 95% CI (0.77–1.67), *P*-value = 0.52, hospital stay HR 0.90, 95% CI (0.65–1.25), *P*-value = 0.53. Lower oxygen levels were successfully achieved during the operative period in the normoxic group. Serum creatinine levels were lower in the normoxic group at day 2, but not on days 1, 3–5. Childhood developmental outcomes were similar. In the year following surgery, 85 serious adverse events were reported (51 normoxic group and 34 hyperoxic group).

CONCLUSIONS: Controlled reoxygenation (normoxic) CPB is safe but with no evidence of a clinical advantage over hyperoxic CPB.

Clinical trial registration number: Current Controlled Trials—ISRCTN81773762.

Keywords: Cardiopulmonary bypass • Cyanosis • Controlled reoxygenation • Clinical trials

ABBREVIATIONS

CI	Confidence interval
CPB	Cardiopulmonary bypass
GMR	Geometric mean ratio
HR	Hazard ratio
ICU	Intensive care unit
PaO ₂	Oxygen partial pressure
PICU	Paediatric intensive care unit
PO ₂	Partial pressure of oxygen
SaO ₂	Oxygen saturation
SD	Standard deviation

INTRODUCTION

Cyanotic children undergoing open-heart surgery are particularly susceptible to reoxygenation injury, arising from the intraoperative reintroduction of high molecular oxygen levels on starting cardiopulmonary bypass (CPB), prior to the ischaemic cardioplegic arrest [1, 2].

One strategy proposed to avoid reoxygenation injury is the use of controlled reoxygenation with an oxygen partial pressure (PaO₂) that is similar to the patient's preoperative oxygen saturation (SaO₂) on starting CPB [3, 4]. Ihnken *et al.* [5, 6] showed the beneficial effects of normoxic reoxygenation in a clinical animal model of acute hypoxaemia and in adult undergoing cardiac surgery. More recently, Peng *et al.* [7] confirmed in an *in vivo* animal model that controlled reoxygenation significantly reduced oxidative stress, inflammation, apoptosis and myocardial injury compared with hyperoxic reperfusion. We also provided direct evidence that controlling reoxygenation can ameliorate the systemic inflammatory and stress response associated with myocardial, cerebral and hepatic injury, particularly in patients with single ventricle physiology [8, 9]. Several studies have recommended that a controlled reoxygenation strategy should be routinely used in cyanotic neonates, infants and children undergoing cardiac surgical repairs that are at high risk of mortality and of developing multiple organ failure after surgery [10–12]. We therefore hypothesized that controlled reoxygenation on starting CPB rather than hyperoxic CPB confers clinical advantages during surgery for congenital cyanotic heart disease. We report the results of the Oxix-2 trial designed to compare the clinical effectiveness of controlled reoxygenation versus hyperoxic CPB for surgery for congenital cyanotic heart disease. We also combine the data from Oxix-2 and a previous trial (Oxix-1), which was conducted at the same institution and followed the same protocol for all end points which were assessed in both studies [8, 9].

METHODS

Trial design

The Oxix-2 trial is a single-centre, parallel-group randomized controlled trial with blinding. Participants were randomized to receive CPB with either standard PaO₂ (150–200 mmHg, hyperoxic group) or controlled PaO₂ (matched to the patient, normoxic group) in a 1:1 ratio. The Oxix-2 trial is registered with Current Controlled Trials (ISRCTN81773762). Patients and the public did not advise on the design, conduct or reporting of this trial. All cyanotic children with SaO₂ of less than or equal to 90% having scheduled surgery to repair or palliate a congenital heart abnormality using CPB were eligible to participate. Children admitted for an emergency operation and those requiring preoperative cardiovascular or respiratory support were excluded. Children who had a preoperative diagnosis of a developmental disorder were eligible to join the trial, but were excluded from the neurocognitive assessments.

The trial was approved by the South West–Central Bristol Research Ethics Committee (reference 07/H0106/172) and the UK Medicines and Healthcare products Regulatory Agency (MHRA, EUDRACT reference 2010-019713-21). MHRA approval was granted in 2010 after the start of the trial, when, after Sponsor review, it confirmed that oxygen is considered an investigational medicinal product in the UK. The University Hospitals Bristol NHS Foundation Trust sponsored the trial.

Interventions

In the hyperoxic group, oxygen levels were maintained at 150–200 mmHg at initiation of CPB and throughout surgery. This was the locally agreed protocol. Oxygen levels of 150–200 mmHg are high compared to the child's usual oxygen levels. In the normoxic group, the CPB was performed using air and minimum oxygen to maintain the patient's own preoperative SaO₂ levels (i.e. <90%). This was achieved by flushing the prime with nitrogen (N₂) just before starting CPB via a bacteriologic filter (0.2 µm) at a rate of between 100 and 200 ml/min while the prime was circulating at 1000 ml/min. An in-line partial pressure of oxygen (PO₂) monitor was used to measure the PO₂ of the prime (in air this will equilibrate at 150 mmHg). The patient's own PO₂ levels were maintained for 10 min, then slowly raised to 120 mmHg by 30 min and 150 mmHg by the end of CPB [8, 9]. All other aspects of the participants' preoperative and postoperative management were in accordance with the hospital local protocols (www.uhbristol.nhs.uk, see [Supplementary Material](#)).

Outcomes

The primary outcomes were (i) duration of inotropic support, (ii) intubation time, (iii) paediatric intensive care unit (PICU) and (iv) postoperative hospital stay (from date of surgery to discharge from cardiac ward). Secondary clinical outcomes were hospital mortality and morbidity measures; blood loss and transfusion requirements; postoperative echocardiographic findings; postoperative blood tests results; renal function as measured by blood urea nitrogen and creatinine levels assessed every 24 h for the first 5 days after surgery; and a childhood developmental assessment using the Bayley Scales of Infant Development (3rd edition, BSID-III).

Sample size

In a pilot study in 32 cyanotic children given hyperoxic CPB, the geometric mean duration of inotropic support was 69 h, with standard deviation (SD) (on the logarithmic scale) 0.61. A sample size of 90 patients per group was required to allow us to detect an 18 h (or equivalently a 26% reduction) in mean duration with 90% power, assuming a 5% level of statistical significance (2-tailed). Using estimates for ventilation time, PICU and hospital stay from the same pilot study, a total sample size of 180 would also be sufficient to detect a 32% reduction in ventilation time (15 h), a 23% reduction in PICU stay (26 h) and a 17% reduction in hospital stay (1.8 days). Clinical outcome data were collected in the earlier Oxix-1 trial ($n = 79$), which was conducted at the same institution and followed the same intervention protocol, and Oxix-2 was designed with the intention that data from both trials should contribute to the total sample size for the primary outcomes, so 101 participants needed to be recruited to Oxix-2. For these outcomes, data from both Oxix-1 and Oxix-2 are used.

Randomization

Randomization was stratified by age (<6 months, ≥ 6 months). Allocations were generated by computer using block randomization with varying block sizes by a statistician independent of the study team. A password-protected secure database concealed allocations until data had been entered to confirm identity and eligibility.

Blinding

Participants and their parents/guardians were blinded to the treatment allocation. Surgeons, anaesthetists, perfusionists and nurses involved in the operation were unblinded. Staff caring for participants in PICU and on the ward were not actively informed of the participant's study allocation. Echocardiographic findings were interpreted by a cardiologist blinded to the treatment allocation. Renal function analysis and developmental assessments using the Bayley Scales of Infant Development were carried out by blinded researchers. All other outcomes were ascertained directly from medical notes, PICU charts and electronic hospital records.

Follow-up

Participants were followed up for safety for 1 year. Serious adverse events after hospital discharge were collected via

questionnaire sent at 3 and 12 months. Where parents/guardians did not respond, safety data were collected via the participant's General Practitioner.

Statistical analysis

Analyses were directed by a pre-specified statistical analysis plan and performed on an intention-to-treat basis. Continuous data are summarized using mean and SD, or median and interquartile range/geometric mean and 95% confidence interval (CI) if distributions are skewed. Categorical data are summarized as number and percentage. Binary outcomes were compared using logistic regression, continuous outcomes using linear regression, time to event outcomes using Cox proportional hazards models (with censoring for death) and continuous longitudinal outcomes using mixed-effects models with patient fitted as a random effect and an unstructured covariance structure for repeated measures. Model fit was assessed via standard methods (e.g. graphical plots) and if inadequate, then transformations were sought. Outcomes analysed on a logarithmic scale were transformed back to the original scale after analysis and results presented as geometric mean ratios (GMRs). All analyses used the hyperoxic CPB as the reference group were adjusted for age (<6 months vs ≥ 6 months) and baseline values where measured. The primary outcome analyses also included trial phase (Oxix-1 or Oxix-2) and treatment \times phase interaction terms in the models and results are presented by phase and overall. Sensitivity analyses were specified in the statistical analysis plan, but not in the trial protocol: (i) replacing intubation time, PICU and hospital stay with the maximum observed time for patients who died, (ii) including any period of reintubation in the intubation time, (iii) reanalysing inotropic data including only dopamine usage, the only inotrope collected in both Oxix-1 and Oxix-2, (iv) imputing missing presurgery developmental scores and (v) modelling baseline and follow-up developmental scores jointly (see [Supplementary Material](#) for further details). One *post hoc* sub-group analysis was conducted, comparing the primary outcomes for participants with more and less severe cyanosis. Outcomes are reported as effect sizes with 95% CIs and likelihood ratio tests were used to determine statistical significance. Analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 13.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Recruitment

Between November 2003 and November 2007, a total of 79 patients consented to participate to the Oxix-1 trial and were randomized (screening data unavailable). Between May 2008 and May 2014, a total of 216 patients were screened for inclusion in the Oxix-2 trial, 49 of whom were found to be ineligible. In total, 169 patients were approached to join the trial and 90 patients agreed, provided written informed consent and their child was randomized (53%). Combining the Oxix-1 and Oxix-2 trials, 83 participants were allocated to the hyperoxic (standard) treatment and 86 to normoxic (experimental) treatment (Fig. 1).

The primary analysis includes all randomized participants, there were no withdrawals. There were 6 treatment cross-overs in the normoxic group and 1 patient in the hyperoxic group was

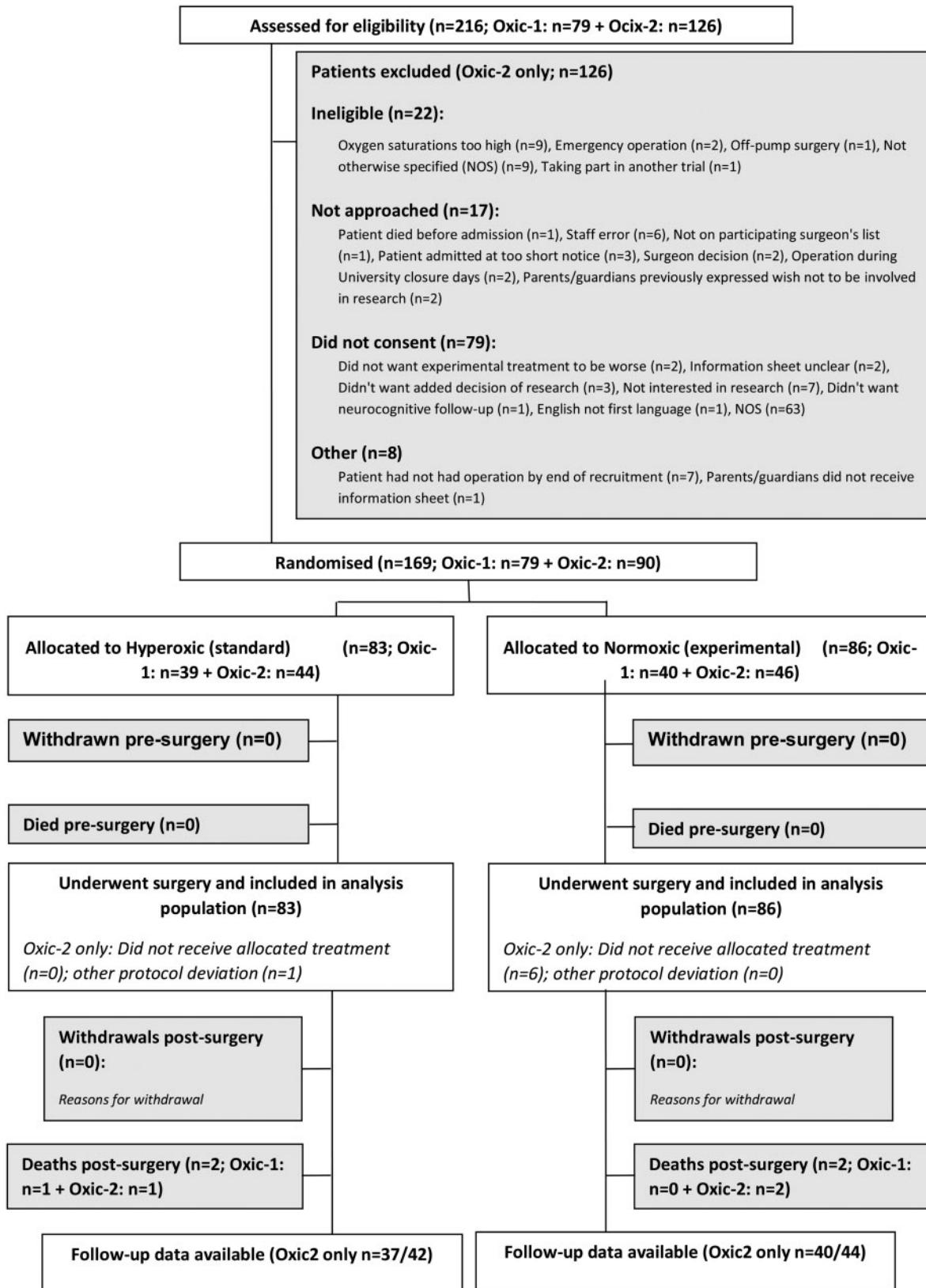


Figure 1: Flow of participants.

randomized and treated but ineligible, as they were participating in another trial (Supplementary Material, Table S1). Oxic-1 participants were followed up to hospital discharge only. Oxic-2

participants were followed up for 12 months after randomization. Safety data to 12 months were collected for 77/90 (86%) Oxic-2 participants.

Table 1: Participant characteristics and operative details

	Oxic2				Oxic1			
	Randomized to hyperoxic (n = 44)		Randomized to normoxic (n = 46)		Randomized to hyperoxic (n = 39)		Randomized to normoxic (n = 40)	
	n	%	n	%	n	%	n	%
Demography								
Age (months), median (IQR)	10.8	(5.6–51.6)	10.4	(5.1–25.2)	14.2	(4.8–51.8)	14.7	(6.1–39.6)
Male gender	28/44	63.6	21/46	45.7	23/39	59.0	26/40	65.0
Height (cm), ^a median (IQR)	72.0	(63.5–102.0)	72.5	(65.0–87.0)	76.0	(67.0–100.0)	75.5	(63.5–94.5)
Weight (kg), median (IQR)	8.7	(6.3–15.6)	8.4	(6.2–12.0)	9.8	(6.4–16.0)	9.2	(6.6–12.8)
Diagnoses/surgery								
TAPVD	0/44	0.0	0/46	0.0	2/39	5.1	2/40	5.0
TCPC	12/44	27.3	10/46	21.7	8/39	20.5	9/40	22.5
TGA	1/44	2.3	1/46	2.2	5/39	12.8	7/40	17.5
TOF	10/44	22.7	12/46	26.1	16/39	41.0	15/40	37.5
Glenn shunt	16/44	36.4	15/46	32.6	8/39	20.5	7/40	17.5
VSD	0/44	0.0	2/46	4.3				
ASD	2/44	4.5	1/46	2.2				
AVSD	0/44	0.0	2/46	4.3				
Damus–Kaye–Stansel	3/44	6.8	3/46	6.5				
Rastelli procedure	3/44	6.8	1/46	2.2				
Mustard operation	0/44	0.0	2/46	4.3				
Tricuspid valve repair	0/44	0.0	2/46	4.3				
Other surgery/diagnoses	3/44	6.8	6/46	13.0				
Other characteristics								
Heart rhythm								
Sinus rhythm	40/42	95.2	46/46	100.0	38/38	100.0	37/37	100.0
AF	1/42	2.4	0/46	0.0	0/38	0.0	0/37	0.0
Heart block	0/42	0.0	0/46	0.0	0/38	0.0	0/37	0.0
Paced	1/42	2.4	0/46	0.0	0/38	0.0	0/37	0.0
Previous cardiac surgery requiring sternotomy	21/33	63.6	18/36	50.0				
O ₂ saturations (%), ^b median (IQR)	81	(75.5–86.0)	79	(76.0–83.0)				
Duration of surgery								
Duration of surgery ^c (min), median (IQR)	207	(167–265)	206	(165–274)				
Duration of bypass (min), median (IQR)	88	(64–121)	104	(66–131)				
Cardioplegia								
Cardioplegia used	23/43	53.5	26/45	57.8	26/39	66.7	28/39	71.8
Cumulative cross-clamp time ^d	69	(40–94)	85	(72–100)	56	(41–74)	52	(33–68)
Other operative details								
Defibrillation	5/42	11.9	2/43	4.7	1/38	2.6	1/35	2.9
Transannular patch used	10/33	30.3	10/36	27.8				
Intraoperative IABP	3/43	7.0	0/46	0.0				
Pacing post bypass	8/42	19.0	7/43	16.3				

Missing data (Oxic2 hyperoxic, Oxic2 normoxic, Oxic1 hyperoxic, Oxic1 normoxic).

^a11 patients (1, 5, 1, 4).

^b73 patients (36, 37, -, -); information was not collected for the first 73 Oxic-2 participants.

^c49 patients (21, 28, -, -).

^d5 patients (0, 5, 0, 0).

AF: atrial fibrillation; ASD: atrial septal defect; AVSD: atrioventricular septal defect; IQR: interquartile range; TAPVD: total anomalous pulmonary venous defect; TCPC: total cavopulmonary connection; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect.

Baseline data

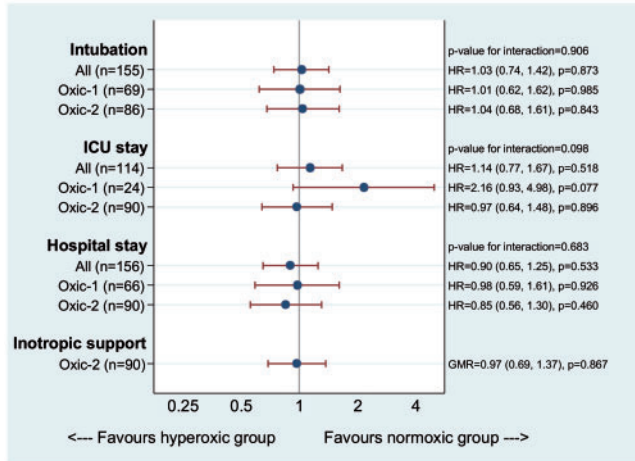
The median age of participants in Oxic-2 was 10.5 months (interquartile range 5.3–40.8) and 49/90 (54%) participants were male. Incidentally, in the hyperoxic group, there were proportionally more male children (64% vs 46%) and a higher proportion who had undergone cardiac surgery previously (64% vs 50%). The majority of participants were undergoing either total cavopulmonary connection (22/90; 24%), tetralogy of Fallot (22/90; 24%) or a Glenn shunt (31/90; 34%). Overall, all characteristics were generally well balanced across the treatment groups (Table 1 and Supplementary Material,

Table S2). Participants in Oxic-1 were on average 3.9 months older and included proportionally more tetralogy of Fallot procedures (31/79, 39%).

Operative details

The CPB and cross-clamp times in Oxic-2 were, on average, 16 min longer in the normoxic group than in the hyperoxic group (CPB duration median 104 vs 88 min; cross-clamp duration median 85 vs 69 min), although the median operation duration was just over 3.5 h in both groups (Table 1 and Supplementary Material, Table S3). Cardioplegia was required for 23/43

Primary outcome results



ICU = Intensive Care Unit, HR = hazard ratio; GMR = geometric mean ratio. Numbers in brackets are the 95% confidence interval.

Figure 2: Primary outcome results. Numbers in brackets are the 95% confidence interval. GMR: geometric mean ratio; HR: hazard ratio; ICU: intensive care unit.

(53%) participants in the hyperoxic group and 26/45 (58%) in the normoxic group. Cross-clamp times were similar in both groups.

Primary outcomes

Treatment estimates for the 4 primary outcomes are shown in Fig. 2. The duration of intubation was similar in the 2 groups [median 20 h in the hyperoxic group vs 19 h in the normoxic group, hazard ratio (HR) 1.03, 95% CI 0.74–1.42; $P=0.873$], and did not differ between Oxic-1 and Oxic-2 ($P=0.906$, Supplementary Material, Table S4). Duration of PICU stay was on average 2 h shorter in the normoxic group (median 49 vs 51 h, HR 1.14, 95% CI 0.77–1.67; $P=0.518$). Postoperative hospital stay was similar in the 2 groups (median 9 days in the hyperoxic group and 10 days in the normoxic group, HR 0.90, 95% CI 0.65–1.25; $P=0.533$), and was similar between Oxic-1 and Oxic-2 ($P=0.683$). All participants in the Oxic-2 trial required inotropic support, with dopamine most frequently used in both groups (Supplementary Material, Table S5). The maximum duration of inotropic support was slightly longer in the normoxic group, but not significantly so (median 37 vs 26 h, GMR 1.03, 95% CI 0.73–1.46; $P=0.867$).

Sensitivity analyses replacing intubation time, PICU and hospital stay with the maximum observed time for patients who died, including any period of reintubation in the intubation time and reanalysing inotropic data considering only dopamine usage did not substantially alter the treatment estimates or change conclusions (Supplementary Material, Tables S6–S8). Results were also similar for the subgroups of participants with more and less severe cyanosis (Supplementary Material, Fig. S1).

Secondary outcomes

There were 3 deaths following surgery, 1 in the hyperoxic and 2 in the normoxic group. Similar numbers of patients experienced 1 or more complication in the period to hospital discharge in the 2 groups (28/46; 61% in the normoxic group vs 22/44; 50% in the hyperoxic group, odds ratio 1.58, 95% CI 0.68–3.65; $P=0.287$,

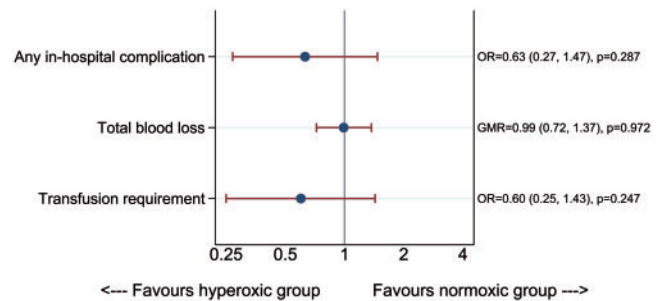


Figure 3: Secondary outcome results. Numbers in brackets are the 95% confidence interval. Oxic-2 trial only. GMR: geometric mean ratio; OR: odds ratio.

PO₂ levels over time

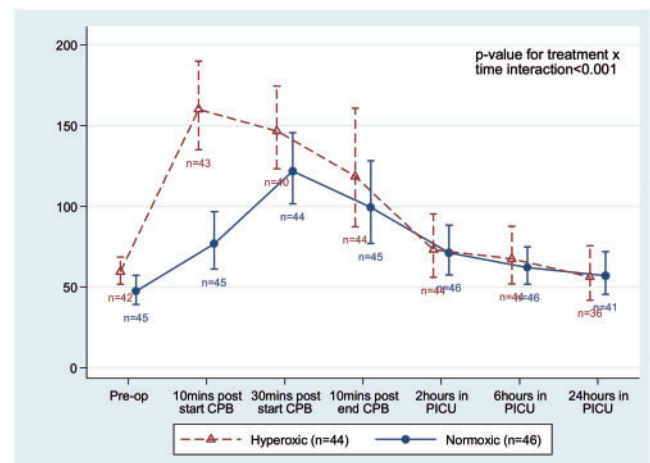


Figure 4: PO₂ levels over time. Treatment estimates (95% CI): 10 min post start CPB GMR = 0.54 (0.43–0.68), 30 min post start CPB GMR = 0.93 (0.77–1.12), 10 min post end CPB GMR = 0.92 (0.63–1.35), 2 h in PICU GMR = 1.10 (0.81–1.48), 6 h in PICU GMR = 1.03 (0.78–1.37) and 24 h in PICU GMR = 1.07 (0.79–1.45). Oxic-2 trial only. CI: confidence interval, CPB: cardiopulmonary bypass; GMR: geometric mean ratio; PICU: paediatric intensive care unit; PO₂: partial pressure of oxygen.

Fig. 3 and Supplementary Material, Table S9). The median total blood loss was similar in both groups (178 ml in the hyperoxic group vs 170 ml in the normoxic group, GMR 1.01, 95% CI 0.73–1.38; $P=0.972$).

Lower oxygen levels (pO₂) were successfully achieved during the operative period for participants in the normoxic group (10 min post start CPB GMR = 0.54, 95% CI 0.43–0.68; 30 min post start CPB GMR = 0.93, 95% CI 0.77–1.12 and 10 min post end CPB GMR = 0.92, 95% CI 0.63–1.35; Fig. 4). Differences in creatinine levels between the groups varied over time (treatment x time interaction $P=0.040$); the mean level was 14% lower in the normoxic group on day 2 (GMR = 0.86, 95% CI 0.75–1.00) (Fig. 5A and Supplementary Material, Table S10). Urea levels were lower in the normoxic group across the first 5 postoperative days, but not significantly so (GMR 0.94, 95% CI 0.83–1.08; $P=0.39$, Fig. 5B and Supplementary Material, Table S10). Serial blood gases measurements and tests carried out as part of usual care are summarized in Supplementary Material, Figs S2–S8; profiles of test results over time were similar between the groups. Few participants had a decrease in ventricular function after surgery (3/25; 12% in the hyperoxic group and 2/27; and 7% in the normoxic group respectively, Supplementary Material, Table S11).

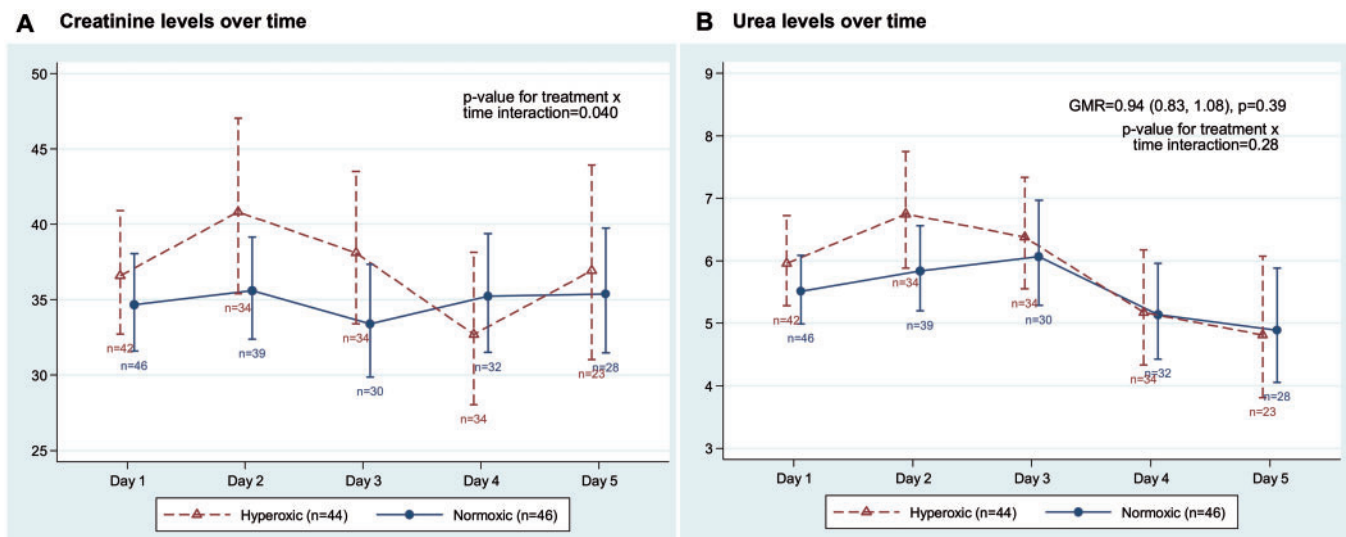


Figure 5: (A) Creatinine levels over time. Treatment estimates [95% confidence interval (CI)]: day 1 GMR = 0.95 (0.83–1.10), day 2 GMR = 0.86 (0.75–1.00), day 3 GMR = 0.93 (0.80–1.08), day 4 GMR = 1.03 (0.89–1.20) and day 5 GMR = 1.02 (0.86–1.19). Oxic-2 trial only. (B) Urea levels over time. Numbers in brackets are the 95% CI. Oxic-2 trial only. GMR: geometric mean ratio.

Follow-up to 1 year

Developmental assessments were carried out on 45 children (24 in the normoxic group and 21 in the hyperoxic group). The assessment is scored in 5 domains, with higher scores indicating more advanced development. No statistically significant differences were found between the 2 groups (Fig. 6, [Supplementary Material, Table S12 and S13](#)). The primary analysis excluded presurgery baseline assessments, which were only available for 20 children. Sensitivity analyses imputing missing baseline scores and restricting the analysis to children with baseline assessments did not substantially alter the treatment estimates or change conclusions ([Supplementary Material, Tables S14 and S15](#)).

In the period from surgery to 1-year, a total of 51 serious adverse events leading to prolonged hospitalization, hospital admission or death were reported in 22 patients in the normoxic group compared 34 events in 12 patients in the hyperoxic group, with infectious or respiratory-related events most commonly reported ([Supplementary Material, Table S16](#)).

DISCUSSION

Together, the 2 Oxic trials provide a combined data set with sufficient power for assessing the clinical effectiveness of controlled reoxygenation in cyanotic infants and children undergoing cardiac surgery. The combined results from the 2 trials suggest that a surgical strategy in which the patient's own preoperative SaO₂ level is maintained at the beginning of CPB and then slowly increased in a controlled graded fashion is safe but with no evidence of a clinical advantage over a strategy of maintaining higher oxygen levels. Inotrope use, intubation time and postoperative stay were similar in the 2 groups, despite the longer average cross-clamp and CPB times in the normoxic group.

There is growing experimental and clinical evidence that reoxygenation injury in a cyanotic environment can be ameliorated by reducing the oxygen levels on starting CPB and then gradually increasing them in a staged manner, as demonstrated by a reduction in oxidative stress and organ injury [1–10, 13–15].

Nevertheless, there remains a lack of reliable data verifying impaired organ function and biochemical parameters closely correlates with poor surgical outcomes. Cyanotic infants and children with congenital heart disease are more likely to suffer renal tubular and glomerular injury, which is exacerbated by reoxygenation injury and prolonged CPB duration [16–18]. Controlling reoxygenation on starting CPB was associated with reduced renal damage in the Oxic-2 trial (lower mean creatinine level on the second postoperative day), confirming the organ protection capacity of this strategy, possibly secondary to reduced oxidative stress [9, 19–21].

Potential concern about hypoxic injury to the brain induced by the low PaO₂ levels during CPB is not supported by the Oxic-2 results, and the neurodevelopment assessments were similar in the 2 groups. Furthermore, the cognitive, motor and adaptive behaviour scores were, on average, slightly higher in the normoxic group, as were the language and social emotion scores up to 3 months, confirming the safety of controlled reoxygenation for brain protection in cyanotic patients undergoing cardiac surgery.

Previous studies have shown that normoxic reperfusion on starting CPB resulted in less myocardial injury as demonstrated by the lower levels of markers such as CPK-MB and Troponin I [8–10, 21]. *In vivo* animal CPB models have also demonstrated improved ventricular function with controlled reoxygenation reperfusion, but this was not observed in Oxic-2 [7]. A possible explanation for this could be that the assessments were based on routinely collected echocardiographic data; detailed parameters of ventricular dysfunction measured in experimental animal settings were not collected.

Limitations

The study has strengths and limitations. Strengths include the inclusive eligibility criteria, with few patients being ineligible and minimization of bias through concealed allocation. Blood samples were analysed in a single hospital laboratory, thereby avoiding inter-laboratory variability, and laboratory personnel conducting the analyses were blinded to the group allocation.

With respect to limitations, participants were recruited from a single centre, thereby limiting the generalizability of the findings.

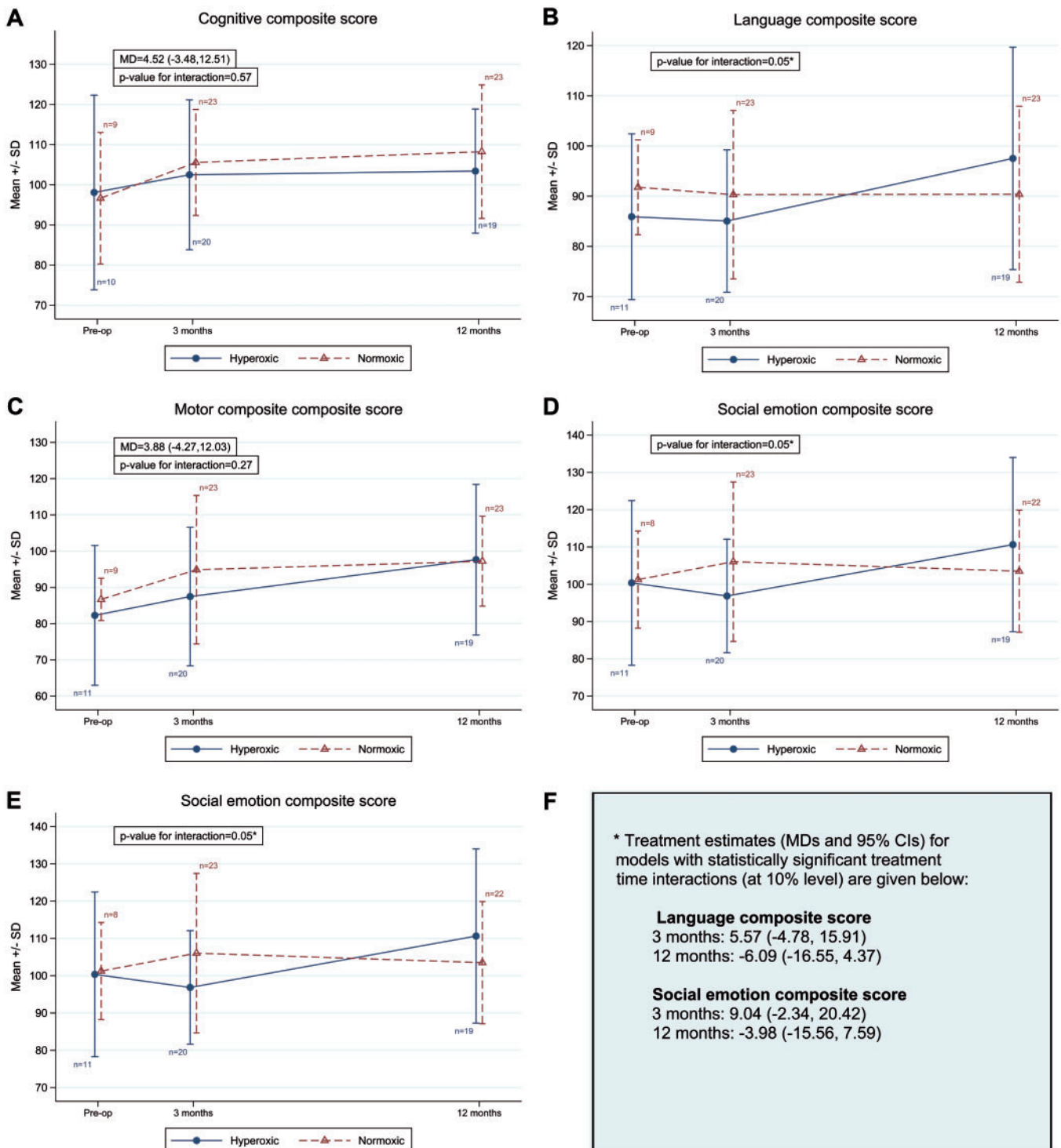


Figure 6: Bayley developmental assessment composite scores. Oxix-2 trial only. CI: confidence interval; MD: mean difference.

The primary outcome analyses included data from the 2 Oxix trials conducted 10-years apart. The total sample was smaller than planned (169 vs target 180 patients) which reduced the power from 90% to 88%. Also, duration of inotropic support and secondary outcomes were only available in Oxix-2 reducing the power of the study further to detect differences between the 2

groups. The primary clinical end points were also subject to variability in intra and postoperative care, but local protocols were followed, and any differences should be balanced between groups. Our failure to assess retinal damage as a possible marker of reoxygenation injury is a further limitation. Early in the trial, the serious adverse event classification of complications in the

postoperative period was not collected, resulting in 56 events not being graded. The lack of blinding of the operating room team is inevitable, but nevertheless represents a weakness of the study.

CONCLUSION

Together, the Oxix-1 and Oxix-2 trials assessed the safety and efficacy of controlled reoxygenation in cyanotic patients undergoing cardiac surgery. The results support previous experimental and clinical reports that controlled reoxygenation is safe, with no statistically significant differences in clinical outcome between the 2 strategies.

SUPPLEMENTARY MATERIAL

[Supplementary material](#) is available at *EJCTS* online.

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Author contributions

Massimo Caputo: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Writing—original draft. **Lauren J. Scott:** Data curation; Formal analysis; Methodology. **Toity Deave:** Formal analysis; Funding acquisition; Methodology; Data collection. **Lucy Dabner:** Project administration. **Andrew Parry:** Conceptualization; Supervision. **Gianni D. Angelini:** Conceptualization. **Karen Sheehan:** Research nurse collecting the data. **Serban Stoica:** Writing—original draft. **Lucy Ellis:** Project administration. **Rosie Harris:** Project administration. **Chris A. Rogers:** Data curation; Formal analysis; Methodology; Validation; Writing—review & editing.

Reviewer information

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