A randomised controlled trial to compare normoxic versus standard cardiopulmonary bypass in cyanotic children undergoing cardiac surgery

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Preliminary report

Abstract

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Myocardial dysfunction remains a leading cause of perioperative morbidity and mortality after successful repair of congenital heart defects. Cyanotic children undergoing heart surgery are particularly susceptible to myocardial reoxygenation injury. One strategy to avoid this injury is the use of controlled re-oxygenation during cardiopulmonary bypass (CPB). This study aims to compare controlled re-oxygenation (normoxic, i.e. normal for a cyanotic child: 70-100 mmHg) and standard (high for a cyanotic child, hyperoxic: 150-200 mmHg) CPB prior to the ischaemic cardioplegic arrest in a parallel group randomised controlled trial. The study was conducted at the Bristol Children's Hospital, a specialist regional centre for paediatric cardiac surgery. Cyanotic children undergoing operations to repair or palliate a heart defect were recruited and followed for 12 months. The primary outcomes were duration of inotropic support, intubation time, time in intensive care and total postoperative stay. A total of 90 children were recruited between 2008 and 2014. 44 were randomised to hyperoxic CPB and 46 to normoxic CPB. The median age was 10.5 months and 54% were male. The characteristics were similar between the groups. On average, the operation lasted just over 3.5 hours in both groups and the bypass time was approximately 90 minutes. On average, the intubation time was 4.4 hours shorter in the normoxic group (median 13.1 hours versus 17.5 hours), but the median duration of ITU stay was similar (50.2 hours versus 50.5 hours). The total hospital stay was on average 1 day longer in the normoxic group (median 10 versus 9 days). The maximum duration of any inotropic support was also longer, on average, for normoxic patients (median 36.5 hours versus 25.5 hours). Three children died following surgery.
Formal comparative analysis is yet to be completed.

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Contents

Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse event
AF	Atrial fibrillation
CI	Confidence interval
CICU	Cardiac intensive care unit
CPB	Cardiopulmonary bypass
CRF	Case report form
ECG	Electrocardiogram
HDU	High dependency unit
HR	Hazard ratio
IABP	Intra-aortic balloon pump
IQR	Interquartile range
LV	Left ventricle
MI	Myocardial infarction
OR	Odds ratio
REC	Research ethics committee
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
TIA	Transient ischemic attack

1. Introduction

1.1 Background and rationale

Current myocardial protection techniques in paediatric cyanotic heart surgery are not ideal [2-7]. Myocardial dysfunction characterised by endothelial damage, reduced cardiac compliance, and subsequent low output syndrome remains a leading cause of perioperative morbidity and mortality after successful repair of congenital heart defects. [2, 3, 7, 10]

We have demonstrated [14] that cyanotic children undergoing open heart surgery are particularly susceptible to ischaemia/reperfusion injury. Part of this injury is thought to have arisen from the intraoperative reintroduction of molecular oxygen upon commencement of hyperoxic CPB, prior to ischaemic cardioplegic arrest – a reoxygenation injury.

Cerebral dysfunction is also a major cause of mortality and morbidity after repair or palliation of congenital cardiac defects in infants and children [17,18], and subtle neurological and cognitive dysfunctions may be evident even among children in whom cardiac repair is completely successful. Transient neurological derangements immediately after CPB occur in as many as 64% of patients when studied within 24 hours of surgery [17,18].

1.1.1 Myocardial reoxygenation injury

There is substantial experimental evidence for the existence of a myocardial reoxygenation injury in the cyanotic, immature heart. Studies of hypoxaemia/ reoxygenation in immature piglets have provided evidence for oxygen-mediated myocardial injury as a result of hyperoxaemia in the setting of previous cyanosis [13]. The immature heart has a higher tolerance to hypoxia, but preceding hypoxia prior to ischaemic cardioplegic arrest results in poor functional recovery and is associated with derangements in several metabolites [8-9]. Hypoxia also reduces the antioxidant reserve capacity, leading to a greater susceptibility to the oxidative stress of ischaemia (e.g. cross-clamping of the aorta) and re-oxygenation [2, 7, 8-10]. Re-introduction of oxygen exacerbates this situation and eventually leads to a reduction in myocardial contractility. This is via the production of free radicals and

subsequent lipid peroxidation, cell damage, mitochondrial dysfunction and enzyme leak [2, 7, 10,11].

Our previous studies have shown that cyanotic children have worse myocardial reperfusion injury and clinical outcomes compared to acyanotic ones following similar periods of ischaemic cardioplegic arrest [14]. In a previous study we have shown that reintroduction of oxygen to cyanotic patients on CPB leads to myocardial damage [1]. In this paper, 29 children with or without hypoxic stress were studied, with myocardial injury assessed by the release of troponin I. All cases underwent a period of at least 30 minutes of hyperoxic CPB on a beating heart. Cyanotic patients exhibited significantly higher levels of troponin I release compared to acyanotic patients. These results suggest that the injury seen following cardioplegic arrest may be in part due to CPB-induced re-oxygenation injury, and this has also been demonstrated in other clinical studies [3, 4, 7].

One of the strategies proposed to avoid this situation is the use of controlled re-oxygenation. This involves starting CPB with a hypoxic prime, until normoxic reoxygenation is started with a substrate-enriched cardioplegia. This has been shown to avoid reoxygenation injury and lead to almost complete functional recovery [15,16]. Ihnken et al showed the beneficial effects of normoxic re-oxygenation in a clinical animal model of acute hypoxemia. The same authors [12] demonstrated that hyperoxic CPB during cardiac operations in adults resulted in oxidative myocardial damage related to oxygen-derived free radicals and nitric oxide. These adverse effects can be markedly limited by reduced oxygen tension management.

The concept of normoxic CPB can therefore be applied to surgical advantage during cardiac operations, especially in paediatric patients undergoing repair of complex cyanotic heart defects. Nevertheless, there is no clinical evidence showing the benefits of these surgical strategies during paediatric heart surgery.

1.2 Aims and objectives

There is a large body of evidence on the effects of re-oxygenation injury in adults or in cyanotic paediatric patients undergoing corrective cardiac surgery and we have

demonstrated that cyanotic children undergoing open heart surgery suffer myocardial damage, assessed by release of troponin I [1]. It is thought that this is due to the introduction of relatively high initial levels of oxygen on cardiopulmonary bypass (CPB) prior to ischaemic cardioplegic arrest. We have also demonstrated that this triggers a significant release of specific markers of organ dysfunction, particularly for very susceptible organs like the brain [20]. This re-oxygenation injury and its detrimental effects on myocardial function may be attenuated by reducing the oxygen tension to normal levels on initiating CPB. Little is known on the effects of controlling re-oxygenation during CPB in children undergoing surgery for congenital cardiac abnormalities, and this can only be addressed in a randomised controlled trial study.

This study aims to compare normoxic (normal for a cyanotic child: 70-100 mmHg) and standard (high for a cyanotic child (relatively hyperoxic): 150-200 mmHg) CPB prior to the ischaemic cardioplegic arrest for children undergoing surgery for congenital cyanotic heart disease in a randomised controlled trial. This study follows on from an earlier trial carried out at our unit which compared the same two interventions (OXIC−1). The primary outcome for OXIC-1, which recruited 90 patients, was biochemical markers of organ injury. Data from that trial suggest that the introduction of relatively high initial levels of oxygen triggers a significant release of specific markers of organ dysfunction, including the brain [20]. However, evidence that lowering the oxygen tension to normal levels when initiating CPB leads to reduced morbidity is still to be established. Clinical outcome data were collected in the OXIC-1 trial and our aim is to pool the data from OXIC-1 and OXIC-2 to determine whether using a lower oxygen level (normal for a cyanotic child) leads to an improved outcome.

This work will provide important information regarding strategies of CPB perfusion which aim to decrease the myocardial and neurological damage that occurs during the initial non-physiological hyperoxic extracorporeal circulation in paediatric cardiac surgery.

2. Methods

2.1 Study design

This study is a single centre, open randomised controlled trial. The trial coordinating centre is the Clinical Trials and Evaluation Unit, University of Bristol and patients were recruited from the University Hospitals Bristol NHS Foundation Trust. The University Hospitals Bristol NHS Foundation Trust sponsored for the trial.

2.1.1 Changes to study design after commencement of the study

There were a number of amendments to the study protocol. The first amendment incorporated the addition of neurological assessments to ascertain if differences in the perfusion oxygenation strategy during cardiac surgery affected neurological outcomes in children. Other changes included approval to approach and consent families/guardians of children who were waiting for cardiac surgery on an inpatient ward, as these patients made up a substantial proportion of the eligible children., revised safety reporting procedures and the addition of follow-up questionnaires to ensure safety information was collected until 12 months post-surgery A myocardial cell contractility sub-study was also added in 2009.

Partway through the study we became aware that an application to the Medicines and Healthcare products Regulatory Agency (MHRA) should be made for a Clinical Trial Authorisation (CTA) because of the use of medical oxygen in the study. The study was temporarily halted whilst the application was made and approval obtained.

2.2 Participants

2.2.1 Eligibility criteria

Cyanotic children having scheduled surgery to repair or palliate a heart abnormality represent the target population. All potential participants presenting to the paediatric cardiac surgery services at University Hospitals Bristol (UH Bristol) were considered to take part in the trial.

Inclusion Criteria

1. Cyanotic children undergoing operations to repair or palliate a heart defect

2. Children must be ≥1 month old to be eligible for all the neurocognitive assessments. Children <1 month old are eligible only for the 3 and 12 month post-operative neurocognitive assessments

Exclusion Criteria

1. Children with a preoperative diagnosis of Down's syndrome or other developmental disorders are excluded from the neurocognitive assessments as part of the trial, but may be included in the main study
2. Patients undergoing emergency operations
3. Children requiring cardiovascular and/or respiratory support prior to study entry

2.2.2 Changes to study eligibility criteria after commencement of the study

Originally, the eligibility criteria stated that children should be 'undergoing operations to repair a heart defect'. This was amended to say 'repair or palliate', primarily as a clarification, as many of the congenital conditions cannot be repaired; only palliated.

Due to difficulties in recruiting, in 2012 the inclusion criteria were extended to include the neonatal population (≤1 month old) as these patients also made up a significant proportion of the eligible cyanotic population. These patients were included in the trial but were not eligible for the neurocognitive assessments (a secondary outcome) at baseline as the instruments were only valid for children over 1 month old. They were eligible for neurocognitive assessments at 3 and 12 months.

Participants with developmental disorders were excluded from the study initially, because of their inability to complete the neurocognitive assessments. However, many cyanotic cardiac conditions are associated with developmental disorders, further reducing our study population. We amended the eligibility criteria to include children with developmental disorders in the main study but excluded them from taking part in the neurocognitive assessments.

2.3 Settings

Patients were recruited to the OXIC-2 study from a single specialist paediatric cardiac surgery centre in the South West UK.

2.4 Interventions

Eligible patients undergoing surgery for congenital cyanotic heart disease whose parents/guardians consented to their participation were randomly allocated to normoxic (normal for child) or standard (relatively hyperoxic) cardiopulmonary bypass (CPB):

- **Standard CPB:** cardiopulmonary bypass with 150-200 mmHg of oxygen (control).
- **Normoxic CPB:** cardiopulmonary bypass with 70-150 mmHg of oxygen (experimental).

All operations were performed using CPB with ascending aortic cannulation and bicaval venous cannulation.

2.4.1 Normoxic CPB.

Air and minimum O_2 required were used to maintain SaO_2 at preoperative levels as much as possible (i.e. to keep SaO_2<95%). A normoxic prime was achieved by flushing the prime with N_2 just before starting CPB and the level of PO_2 in the prime of the CPB was kept as close as possible to the pre-operative patient's PO_2. Hence an initial N_2 flush was used, followed by CPB in air which keeps the PO_2 at preoperative levels. We aimed for the patient's own PO_2 for 10 minutes, then slowly raised the PO_2 to 120mmHg by 30 minutes and 150mmHg by the end of CPB.

2.4.2 Standard CPB

This is the current standard regimen and should be conducted according to the UH Bristol CPB protocol. Oxygen is run at 100% to maintain SaO_2 at >95% and the PO_2 levels of 150 to 200mmHg when starting CPB.

2.5 Outcomes

2.5.1 Primary outcome

The primary outcome comprises duration of inotropic support, intubation time, time in the intensive care unit (ICU) and total postoperative stay.

2.5.2 Secondary outcomes

Secondary outcomes include:

(a) In-hospital mortality and other standard measures of morbidity as used in previous RCTs, e.g. blood loss and transfusion requirement, abnormal echocardiographic findings, abnormal postoperative blood tests results.

(b) Developmental assessment using the Bayley Scales of Infant Development (3rd edition, BSID-III) measured preoperatively (where possible) and at 3 and 12 months after surgery. This is an individually administered instrument, designed for use in infants aged 1−42 months, which assesses the current developmental functioning of babies and children. It comprises three major parts that are tested with the child: Cognitive, Language, and Motor. A questionnaire completed by the parent/caregiver looks at the child's Social-Emotional and Adaptive Behaviour development.

   a. The Cognitive Scale looks at how the child thinks, reacts, and learns about the world around him or her.

   b. The Language scale has two parts. The Receptive Communication (RC) part looks at how well the child recognises sounds and how much the child understands spoken words and directions. The Expressive communication part looks at how well the child communicates using sounds, gestures, or words.

   c. The Motor scale has two parts. The Fine Motor part looks at how well the child can use his or her hands and fingers to make things happen. The Gross Motor part looks at how well the child can move his or her body.

   d. The Social-Emotional part of the parental questionnaire assesses development in infants and young children by identifying social-emotional milestones that are normally achieved by certain ages.

   e. The Adaptive Behaviour portion of the questionnaire asks caregivers to respond to items that assess their child's ability to adapt to various demands of normal daily living.

(c) Renal function as measured by urea nitrogen and creatinine levels. Measurements were taken every 24 hours for the first 5 days after surgery. CPB has been shown to be potentially damaging for kidneys, but there is little clinical data on the effects of reoxygenation injury on renal function.

(d) Gene expression profiles associated with reoxygenation injury to the heart muscle and cell contractility associated with reoxygenation injury to the heart muscle measured in heart tissue left over from the surgery and considered clinical waste.

2.5.3 Adverse events

Post-operative adverse events were collected on the study Case Report Forms (CRFs) by the study research nurse or study coordinator, until the time of hospital discharge. The CRFs that collected adverse events changed over the course of the study (i.e. earlier versions of the CRF collected less adverse event information). The changes were partly due to changes in regulatory requirements and improved internal reporting processes. At the end of the study, retrospective adverse event data collection took place on the participants who had inadequate safety information collected according to the standards employed at the end of the study.

Additional safety data were collected post-discharge until 12 months after the child's operation, via questionnaires sent to the parents/guardians. If no response was received, a request was sent to the patient's General Practitioner (GP) for the information. **This process is currently ongoing at the time of this report.**

Adverse events are frequent and common in paediatric cardiac surgery. To avoid over-reporting, a list of 'expected events' was introduced during the course of the study. Before this time, all events that satisfied the seriousness criteria were reported to the Sponsor and regulatory authorities (if appropriate). After the 'expected events' list was introduced, the research team only notified fatal and 'unexpected' non-fatal Serious Adverse Events to the Sponsor. Unexpected events are those not listed in the trial protocol or on the CRFs.

2.5.4 Changes to study outcomes after commencement of the study

Initially, astroglial protein S100, measured in the blood, was included as a secondary outcome. This outcome was subsequently removed as we were unable to accrue sufficient patients/samples to form batches to be analysed within the 3-4 month time-frame before sample degradation. It was not cost-effective to analyse the samples and there were also issues of obtaining access to the laboratory equipment and staff to perform the tests.

We intended to seek the school entry test results of participants. This has not been done. Many of the children who participated were <1 year old at study entry. Therefore we would have to wait until the youngest participant reaches school age before we could obtain the results on all participants (2017). In addition, obtaining the school entry tests from multiple local education authorities (LEAs) – due to our centre covering a very wide geographical area and the study population frequently moving to new areas – or from the parents may not be possible. School entry tests have also changed over the years which could make interpretation of the results difficult.

2.6 Sample size

2.6.1 Primary outcomes

In a pilot study in 32 cyanotic children given hyperoxic CPB, the geometric mean duration of inotropic support was 69 hours, with standard deviation (on the logarithmic scale) 0.61. A sample size of 90 patients per group would be sufficient to allow us to detect a clinically relevant 26% or greater reduction in mean duration (equivalent to reduction of 18 hours) with 90% power, assuming a 5% level of statistical significance (2−tailed).

Using estimates for ventilation time, ICU 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 hours), a 23% reduction in ICU stay (26 hours), and a 17% reduction in hospital stay (1.8 days). All these differences represent clinically relevant reductions.

In the earlier trial comparing the same two interventions (OXIC−1) 90 participants were recruited and clinical outcome data were also collected. It was intended that 90 patients be recruited to OXIC−2 and that the clinical data from the two studies be bought together for assessment of the clinical outcomes, giving a total sample of 180 patients for analysis.

2.6.2 Secondary outcomes

This sample size of 90 participants is sufficient to detect the following differences in secondary outcomes with 90% power:

(a) 8.5 points on the Bayley scales; data from OXIC-1 suggested that two thirds of the children recruited (i.e. 60 children) would be eligible for the developmental assessment pre-operatively

and at 3 and 12 months after surgery (i.e. they will be no more than 42 months of age 12 months after surgery). A study in 54 children (27 per group, allowing for approx. 10% loss to follow-up) is sufficient to detect a difference of 8.5 points on the Bayley scales, adjusting for preoperative scores, assuming a correlation of 0.7 between pre- and post-measurements. This magnitude of difference represents 0.53 standard deviations (based on normative data), i.e. a moderate effect size.

(b) 0.36 standard deviations in serum creatinine and urea nitrogen, assuming correlations of 0.7 between the pre- and post-measures and between the 5 post-measures.

(c) 0.69 standard deviations in continuous measures such as blood loss

(d) Sample size for the gene expression study was set at 32 patients (16 per group, 2 samples per patient) based on previous studies. Data from the first 12 patients recruited will be used to assess the significance of the differentially expressed genes. (An Affymetrix GeneChip array found a statistically significant result using 4 patients per group. Samples from the remaining 20 patients will be used to validate the microarray data using different techniques (e.g. quantitative real-time PCR to test whether the intervention alters the mRNA expression level of candidate genes as indicated by microarray analysis).

(e) Sample size for the contractility study - 16 patients (8 per group, 2 samples per patient) was chosen on the basis of previous studies [22].

2.7 Randomisation

Participants were randomly assigned in a 1:1 ratio and stratified by age (<6months vs. ≥6months). Random allocations were generated by computer using block randomisation with varying block sizes. The allocation sequence was prepared in advance of the study by a statistician independent of the study team and was kept concealed from all members of the research team throughout the course of the study. The research team was unable to predict the next allocation in the sequence due to varying block sizes and allocation sequence concealment, thus avoiding selection bias. Allocations were obtained by the study coordinator(s) using a secure password-protected web-based interface. The randomisation procedure was performed as close as possible to the time of the participants' surgery. Where a child's surgery was unexpectedly rescheduled, they would retain their randomised allocation.

2.8 Blinding

Surgeons, anaesthetists, perfusionists and nurses were not blinded as these staff groups were present in theatre when the intervention was being applied and it would have been possible to determine which allocation the participant had received. However, the child, their parents/guardians, and the researcher who carried out the neurocognitive assessments were blinded to the allocation. In order to test the success of blinding, the researcher was required to make a decision about the allocation of the patient before starting and at the end of each psychometric assessment; these data will allow the study to comply with internationally recognised reporting standards [19].

2.9 Data collection

Data to characterise the patients who were identified and approached about the trial (e.g. eligibility criteria, key demographic data, willingness to participate) was collected by the trial co-ordinator or research nurse on pre-printed forms.

Data on enrolled trial participants was collected pre-operatively (during their pre-assessment clinic visit or during the patients' hospital admission for heart surgery), during their hospital stay (until discharged from hospital), and at 3 and 12 months. During their hospital stay, data was collected on the primary outcome, along with potential confounding factors, adverse events and where appropriate, data on the secondary outcomes. Data was collected from the patient's clinical records and from other data sources such as print-outs from theatre equipment. Data was collected on pre-printed Case Report Forms (CRFs) by a Research Nurse and were entered onto a password-protected computerised database by the study coordinator.

For those participants who were eligible for the neurocognitive assessments, the researcher performed the pre-operative assessments and collected the data either at the child's home or at the hospital (if the family preferred it or if the child was an in-patient). Data were subsequently collected at the post-operative assessments at 3 and 12 months, either at the child's home, or an alternative location suitable for the parents/guardians. A component part of each assessment was a self-completed questionnaire by the parents/guardians, which was sent out prior to the assessment date, with a spare copy taken by the researcher to the assessment appointment, to use as necessary.

Data for the neurocognitive assessments were collected on pre-printed forms and assessment forms provided by the Bayley Scale of Infant Development tool.

Adverse events were collected on CRFs until hospital discharge and by postal questionnaire to the parents/guardian at 3 and 12 months. For non-responders of the questionnaires, the last known GP was contacted for information on the participant's hospital admissions for the time between last contact with the research team and 12 months after their heart surgery.

Waste heart tissue samples for the gene expression and contractility study were collected immediately after institution of CPB and again just prior to the application of the aortic cross-clamp (approximately 30 minutes after starting CPB). For the gene expression study tissue samples were immediately put in RNAlater solution (Qiagen, UK) until RNA extraction could take place. Tissue collected for contractility was put in cold cardioplegia and transferred to the laboratory for cell isolation using an established enzymatic digestion technique. All samples were labelled with a unique anonymised identifier (trial number) and the point during the operation when the sample was taken.

2.10 Statistical methods

Continuous data are summarised as means and standard deviations (or as medians and interquartile ranges (IQR) if distributions are skewed), and categorical data are summarised as a number and percentage. Summaries are presented as intention to treat, i.e. patients who crossed over are summarised by the treatment they were randomised to, not the treatment they received. Additionally, adverse event data are described according to the treatment received. Formal comparative analyses, which will bring together the data from the previous OXIC-1 study with OXIC-2 are yet to be undertaken.

3. Results

3.1 Screened patients

216 potential participants were screened for inclusion in the study. 126 patients were excluded: 22 were ineligible, 17 were not approached, 79 did not consent and 8 patients had 'other reasons'. See Figure 1, Flow of Participants, for more details.

3.2 Recruitment

90 patients were recruited and randomised between May 2008 and May 2014. The last follow-up visit took place in June 2015. In total, 44 were randomised to the hyperoxic group and 46 to the normoxic group.

3.2.1 Recruitment rate

Recruitment was variable over time (see Figure 2) and took longer than anticipated. Reasons for the log recruitment period were varied and included lack of operating theatre space and/or available ICU or ward beds and fewer eligible patients than predicted when the study was set-up. Additionally, recruitment was halted for 6 months, from March to August 2010, when the Sponsor and study team became aware that a Clinical Trial Authorisation (CTA) was required.

3.3 Patient withdrawals

No patient withdrew from the study.

3.4 Protocol deviations

Seven protocol deviations occurred during the course of the trial, the majority of which were participants in the normoxic arm that received the standard intervention (hyperoxic) (see Table 1). Reasons for this varied: some were attributed to a clinical decision by the surgeon or perfusionist, others were due to staff error. One patient was recruited but subsequently found to be ineligible due to participation in another clinical trial, but was treated as part of OXIC-2. They were randomised to receive standard treatment and their data are included

Figure 1 Flow of participants

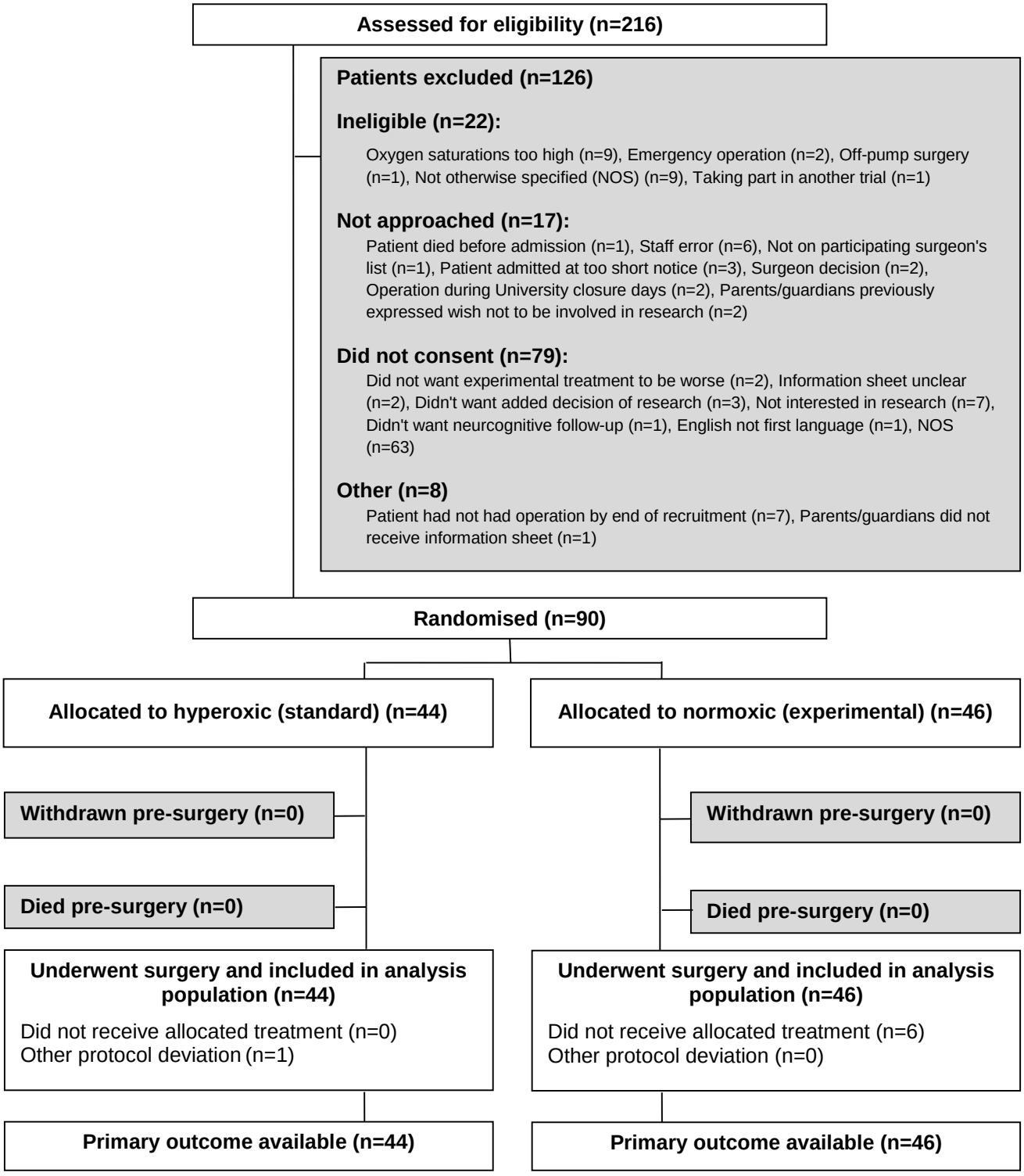


Figure 2 OXIC-2 recruitment

Table 1 Protocol deviations

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	**%**	**n**	**%**	**n**	**%**
Any protocol deviation	1/43	2.3%	6/44	13.6%	7/87	8.0%
Patient received alternative treatment to that allocated*	0/43	0.0%	6/45	13.3%	6/88	6.8%
Patient ineligible but treated in the trial**	1/44	2.3%	0/45	0.0%	1/89	1.1%
Patient randomised but not treated in the trial	0/44	0.0%	0/46	0.0%	0/90	0.0%

* Data missing for 2 patient, ** data missing for 1 patient

3.5 Patient follow-up

Overall 59 participants were eligible for the neurocognitive assessments at 3 and 12 months after surgery. At 3 months 46/59 assessments were completed and at 12 months 44/59 assessments were completed. Reasons for the assessments not being undertaken were i) unable to contact family (3 at 3 months, 4 at 12 months), ii) parents refused (2), iii) parents not contacted about neurocognitive assessments (2), iv) participant died (1), v) limited English (1), vi) not recorded (4 at 3 months, 5 at 12 months)

3.6 Numbers analysed

The analysis population includes all cyanotic children who received surgery to repair or palliate a heart abnormality, who met the inclusion criteria and were randomised into the study (see Figure 1 for details).

3.7 Baseline data and operative characteristics

The demographics and clinical characteristics of the 90 randomised participants is shown in Table 2. Overall, the median age of the participants was 10.5 months, and 54% were male. By chance, there were proportionally more male children allocated to the hyperoxic group (64% versus 46%) and proportionally more who had undergone cardiac surgery previously (64% versus 50%). A significant proportion of the study participants were on medication pre-surgery (aspirin, 41%, beta blockers 22%, ACE inhibitors 21%). The oxygen saturation at recruitment was similar in the two groups.

Operative characteristics are summarised in Table 3. On average, the operation lasted just over 3 and half hours in both groups and the bypass time was approximately 90 minutes. Overall, 56% of the procedures required cardioplegia, with a median cross-clamp time of 83 minutes (IQR 61 to 97 minutes). The bypass and cross-clamp times were on average, 16 minutes longer in the normoxic group.

Table 2 Patient demography and past history

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	**%**	**n**	**%**	**n**	**%**
DEMOGRAPHY						
Gender (male)	28/44	63.6%	21/46	45.7%	49/90	54.4%
Age (months; median, SD)	10.5	(5.5, 51.5)	10.5	(5.0, 25.0)	10.5	(5.0, 41.0)
Height (cm; median, SD) *	72.0	(63.5, 102.0)	72.5	(65.0, 87.0)	72.3	(64.9, 91.8)
Weight (kg; median, SD)	8.7	(6.3, 15.6)	8.4	(6.2, 12.0)	8.4	(6.2, 14.7)
DRUGS ON ADMISSION						
Beta blockers	9/44	20.5%	11/46	23.9%	20/90	22.2%
Diagoxin	0/44	0.0%	0/46	0.0%	0/90	0.0%
Diuretics	8/44	18.2%	7/46	15.2%	15/90	16.7%
ACE inhibitors	8/44	18.2%	11/46	23.9%	19/90	21.1%
Calcium channel blockers	0/44	0.0%	0/46	0.0%	0/90	0.0%
Nitrates	0/44	0.0%	1/46	2.2%	1/90	1.1%
Aspirin	20/44	45.5%	17/46	37.0%	37/90	41.1%
Warfarin	0/44	0.0%	0/46	0.0%	0/90	0.0%
Nicorandil	0/44	0.0%	0/46	0.0%	0/90	0.0%
Other drugs	15/44	34.1%	17/46	37.0%	32/90	35.6%
OTHER DETAILS						
Heart rhythm						
Sinus	40/42	95.2%	46/46	100.0%	86/88	97.7%
Atrial flutter	1/42	2.4%	0/46	0.0%	1/88	1.1%
Paced	1/42	2.4%	0/46	0.0%	1/88	1.1%
Previous cardiac surgery requiring sternotomy	21/33	63.6%	18/36	50.0%	39/69	56.5%
O2 saturations (median, IQR) **	81	(75.5, 86.0)	79	(76.0, 83.0)	80	(76.0, 84.0)

Table 3 Intra operative details

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	%	n	n	%	n
BYPASS DETAILS						
Operation duration (mins; median, IQR) *	207	(167, 265)	206	(165, 274)	207	(167, 265)
Bypass duration (mins; median, IQR)	88	(64, 121)	104	(66, 131)	93	(65, 127)
Haemodynamic instability prior to CPB	4/44	9.1%	6/45	13.3%	10/89	11.2%
Cardioversion	5/43	11.6%	4/45	8.9%	9/88	10.2%
Ischemic changes when coming off CPB	1/41	2.4%	2/39	5.1%	3/80	3.8%
Modified ultrafiltration	8/33	24.2%	8/35	22.9%	16/68	23.5%
CARDIOPLEGIA DETAILS						
Cardioplegia	23/43	53.5%	26/45	57.8%	49/88	55.7%
If yes, time from starting cardioplegia to ECG arrest (mins; median, IQR) **	43	(20, 60)	35	(25, 51)	40	(24, 51)
If yes, did heart distend during cardioplegia?	3/19	15.8%	1/21	4.8%	4/40	10.0%
If yes, cumulative cross-clamp time (median, IQR) ***	69	(40, 94)	85	(72, 100)	83	(61, 97)
Rhythm on cross clamp removal						
Sinus	19/23	82.6%	23/25	92.0%	42/48	87.5%
Atrial fibrillation	1/23	4.3%	0/25	0.0%	1/48	2.1%
Heart block	2/23	8.7%	2/25	8.0%	4/48	8.3%
Ventricular tachycardia	1/23	4.3%	0/25	0.0%	1/48	2.1%
OTHER DETAILS						
Transannular patch used	10/33	30.3%	10/36	27.8%	20/69	29.0%
Defibrillation	5/42	11.9%	2/43	4.7%	7/85	8.2%
Intraoperative IABP	3/43	7.0%	0/46	0.0%	3/89	3.4%
Pacing post bypass	8/42	19.0%	7/43	16.3%	15/85	17.6%

*Data missing for 49 patients (21, 28). **Data missing for 11/49 patients (5, 6). ***Data missing for 5/49 patients (0, 5).

3.8 Primary outcome

Primary outcome data are summarised in Table 4. On average, the intubation time was 4.4 hours shorter in the normoxic group (median 13.1 hours versus 17.5 hours), but the median duration of ITU stay was similar (50.2 hours versus 50.5 hours and the total hospital stay was on average 1 day longer in the normoxic group (median 10 versus 9 days). The maximum duration of any inotropic support was also longer, on average, for normoxic patients (median 36.5 hours versus 25.5 hours). However all patients required inotropic support and the number of patients requiring each type of inotropic support was similar in the two groups (see Table 4).

Table 4 Primary outcomes

	Randomised to Hyperoxic (n=44)		**Randomised to Normoxic (n=46)**		**Overall (n=90)**	
	median	**IQR**	**median**	**IQR**	**median**	**IQR**
Total intubation duration (hours) *	17.5	(8.8, 51.7)	13.1	(8.7, 44.0)	16.5	(8.8, 47.2)
Initial intubation duration (hours) *	17.0	(8.5, 35.8)	13.1	(8.7, 33.4)	14.5	(8.6, 33.4)
ITU stay (hours) *	50.5	(27.7, 116.3)	50.2	(41.8, 117.5)	50.5	(36.0, 117.5)
Duration of postoperative hospital stay (days) *	9.0	(7.0, 12.0)	10.0	(7.0, 14.0)	9.0	(7.0, 13.0)
Any post-operative inotropic support	44/44	100.0%	46/46	100.0%	90/90	100.0%
Maximum duration of post-operative inotropic support (hours)	25.5	(19.0, 69.5)	36.5	(21.0, 62.0)	28.5	(20.0, 67.0)
Adrenaline (n, %)	4/44	9.1%	3/46	6.5%	7/90	7.8%
If yes, duration (hours)	17.5	(7.5, 64.0)	12.0	(6.0, 36.0)	12.0	(6.0, 36.0)
Noradrenaline (n, %)	4/44	9.1%	2/46	4.3%	6/90	6.7%
If yes, duration (hours)	42.0	(11.5, 191.5)	22.5	(19.0, 26.0)	22.5	(14.0, 70.0)
Dopamine (n, %)	40/44	90.9%	43/46	93.5%	83/90	92.2%
If yes, duration (hours)	20.0	(12.0, 40.5)	23.0	(17.0, 44.0)	21.0	(13.0, 44.0)
Milrinone (n, %)	39/44	88.6%	42/46	91.3%	81/90	90.0%
If yes, duration (hours)	26.0	(19.0, 87.0)	38.0	(21.0, 66.0)	34.0	(20.0, 70.0)
Dobutamine (n, %)	1/44	2.3%	0/46	0.0%	1/90	1.1%
If yes, duration (hours)	37.0	(37.0, 37.0)			37.0	(37.0, 37.0)
Enoximone (n, %)	0/44	0.0%	0/46	0.0%	0/90	0.0%

3.9 Secondary outcomes

3.9.1 In hospital morbidity

In-hospital morbidity was defined in the protocol as blood loss and transfusion requirement, abnormal echocardiographic findings, or abnormal postoperative blood tests results. The results for these outcomes are summarised in Tables 5 and 6 and Figures 3 to 12. The median total blood loss was similar in both groups (178ml in the normoxic group versus 170ml in the hyperoxic group), although the transfusion rate was slightly higher in the normoxic group (43% in the normoxic group versus 32% in the hyperoxic group). Overall, 37% of children required at least one red blood cell (RBC) transfusion, 11% required fresh frozen plasma (FFP) and 13% needed a platelet transfusion after surgery.

Table 5 Blood loss and transfusion requirement

	Randomised to Hyperoxic (n=44)		**Randomised to Normoxic (n=46)**		**Overall (n=90)**	
	n	**%**	**n**	**%**	**n**	**%**
Total blood loss (median, IQR)	178	(93, 245)	170	(105, 280)	175	(100, 250)
Any transfusions	14/44	31.8%	20/46	43.5%	34/90	37.8%
RBC units						
0	32/43	74.4%	32/45	71.1%	64/88	72.7%
1	9/43	20.9%	11/45	24.4%	20/88	22.7%
2	2/43	4.7%	2/45	4.4%	4/88	4.5%
FFP units						
0	40/44	90.9%	39/45	86.7%	79/89	88.8%
1	4/44	9.1%	4/45	8.9%	8/89	9.0%
2	0/44	0.0%	2/45	4.4%	2/89	2.2%
Platelet units						
0	39/44	88.6%	39/46	84.8%	78/90	86.7%
1	3/44	6.8%	7/46	15.2%	10/90	11.1%
2	2/44	4.5%	0/46	0.0%	2/90	2.2%

Echocardiographic results are summarised in Table 6. Few patients had a decrease in left or right ventricular function from baseline to after surgery (although these data were not collected for a significant number of patients).

Table 6 Echocardiographic findings

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	**%**	**n**	**%**	**n**	**%**
Abnormal LV function*	2/37	5.4%	1/40	2.5%	3/77	3.9%
Abnormal in RV function*	2/27	7.4%	2/30	6.7%	4/57	7.0%
Abnormal in LV or RV function*	3/25	12.0%	2/27	7.4%	5/52	9.6%
PRE-OPERATIVE						
LV function						
Good	30/34	88.2%	32/35	91.4%	62/69	89.9%
Mildly impaired	4/34	11.8%	3/35	8.6%	7/69	10.1%
Moderately impaired	0/34	0.0%	0/35	0.0%	0/69	0.0%
Severely impaired	0/34	0.0%	0/35	0.0%	0/69	0.0%
RV function						
Good	14/15	93.3%	21/24	87.5%	35/39	89.7%
Mildly impaired	1/15	6.7%	3/24	12.5%	4/39	10.3%
Moderately impaired	0/15	0.0%	0/24	0.0%	0/39	0.0%
Severely impaired	0/15	0.0%	0/24	0.0%	0/39	0.0%
RVOT velocity given	10/43	23.3%	11/45	24.4%	21/88	23.9%
If yes, velocity (median, IQR)	4.0	(3.5, 4.6)	4.3	(4.0, 4.8)	4.1	(3.9, 4.7)
TR velocity recorded	5/43	11.6%	2/45	4.4%	7/88	8.0%
If yes, velocity (median, IQR)	1.8	(0.0, 3.2)	1.8	(0.0, 3.5)	1.8	(0.0, 3.5)
24 HOURS POST-OPERATIVE						
LV function						
Good	24/26	92.3%	24/26	92.3%	48/52	92.3%
Mildly impaired	1/26	3.8%	1/26	3.8%	2/52	3.8%
Moderately impaired	1/26	3.8%	1/26	3.8%	2/52	3.8%
Severely impaired	0/26	0.0%	0/26	0.0%	0/52	0.0%
RV function						
Good	17/21	81.0%	17/22	77.3%	34/43	79.1%
Mildly impaired	2/21	9.5%	4/22	18.2%	6/43	14.0%
Moderately impaired	2/21	9.5%	1/22	4.5%	3/43	7.0%
Severely impaired	0/21	0.0%	0/22	0.0%	0/43	0.0%
RVOT velocity given	6/34	17.6%	7/33	21.2%	13/67	19.4%
If yes, velocity (median, IQR)	2.2	(2.0, 2.5)	3.0	(2.0, 3.8)	2.5	(2.0, 3.8)
TR velocity given	1/34	2.9%	3/33	9.1%	4/67	6.0%
If yes, velocity (median, IQR)	3.0	(3.0, 3.0)	1.0	(0.0, 1.8)	1.4	(0.5, 2.4)

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	**%**	**n**	**%**	**n**	**%**
HOSPITAL DISCHARGE						
LV function						
Good	32/34	94.1%	38/39	97.4%	70/73	95.9%
Mildly impaired	2/34	5.9%	1/39	2.6%	3/73	4.1%
Moderately impaired	0/34	0.0%	0/39	0.0%	0/73	0.0%
Severely impaired	0/34	0.0%	0/39	0.0%	0/73	0.0%
RV function						
Good	21/24	87.5%	25/27	92.6%	46/51	90.2%
Mildly impaired	2/24	8.3%	2/27	7.4%	4/51	7.8%
Moderately impaired	1/24	4.2%	0/27	0.0%	1/51	2.0%
Severely impaired	0/24	0.0%	0/27	0.0%	0/51	0.0%
RVOT velocity given	10/42	23.8%	13/44	29.5%	23/86	26.7%
If yes, velocity (median, IQR)	2.2	(2.0, 2.6)	2.8	(2.0, 3.6)	2.2	(2.0, 3.6)
TR velocity given	8/42	19.0%	4/44	9.1%	12/86	14.0%
If yes, velocity (median, IQR)	3.2	(2.7, 3.5)	2.8	(1.3, 3.5)	3.0	(2.5, 3.5)

* defined as post-operative function as declined follow-up surgery compared to the pre-operative function or the function has not changed since surgery and is classified as mild, moderate or severe impairment. The change in function was measured at discharge when given or at 24 hours if not recorded at discharge.

Median changes in blood gases over time are shown in Figures 3 to .10. Figure 3 shows that lower oxygen levels (pO2) were successfully achieved during the operative period for patients in the normoxic group. For pH, lactate, cBase, sO2, glucose and haemoglobin, patterns were similar in the two groups. By chance, CO2 levels appear to have been were higher in the normoxic group at baseline, but levels were similar between the treatment groups by 24 hours after surgery.

Figure 3 pO2 levels over time

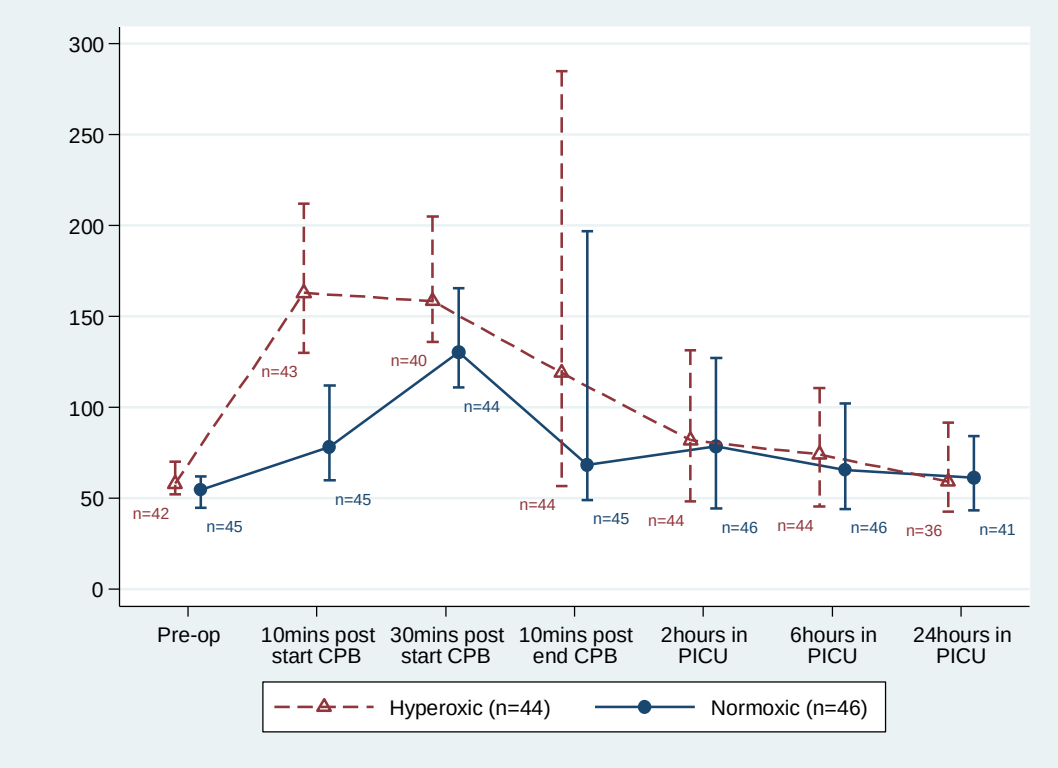


Figure 4 pH levels over time

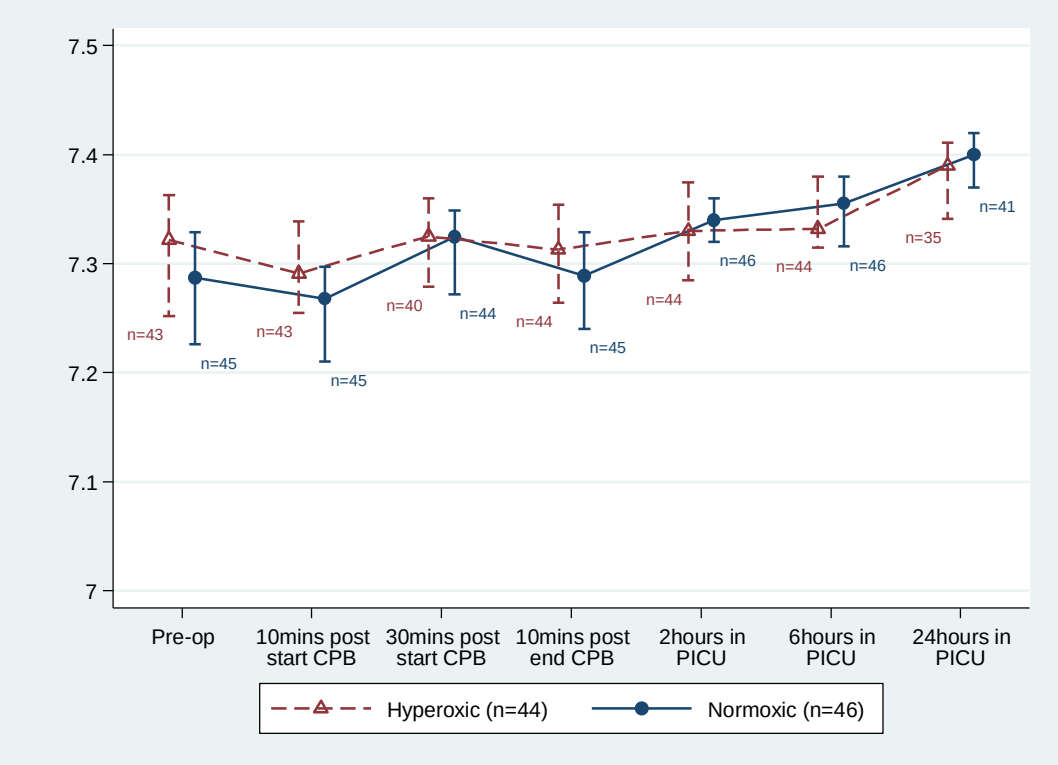


Figure 5 CO2 levels over time

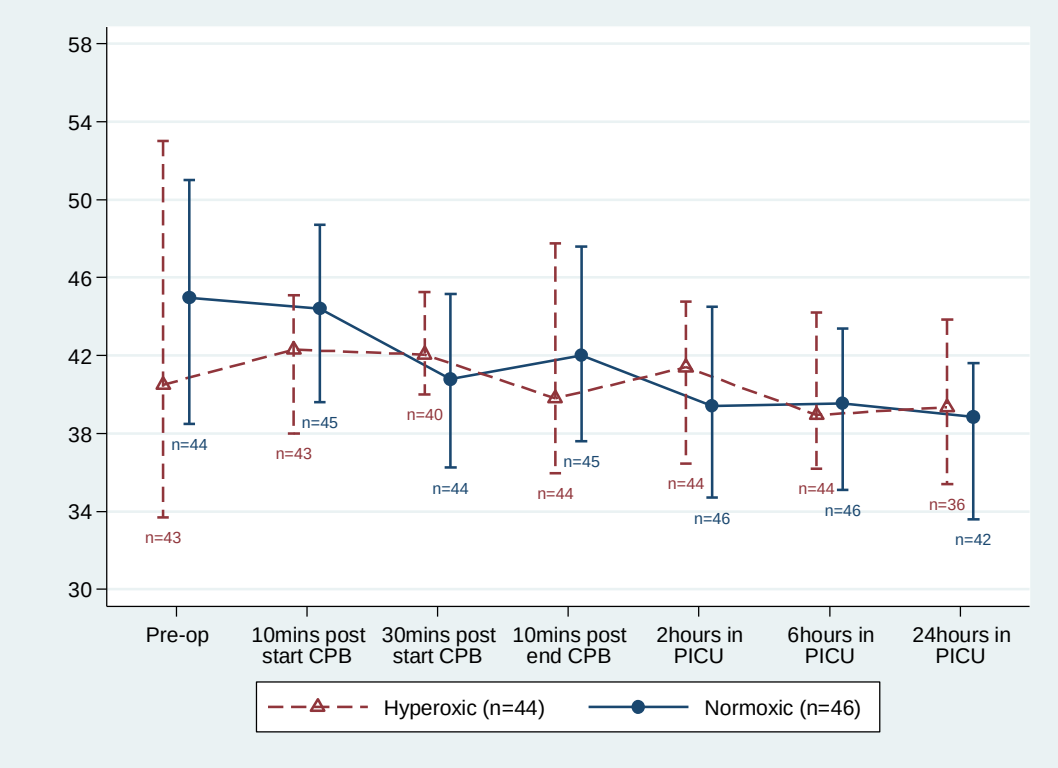


Figure 6 Lactate levels over time

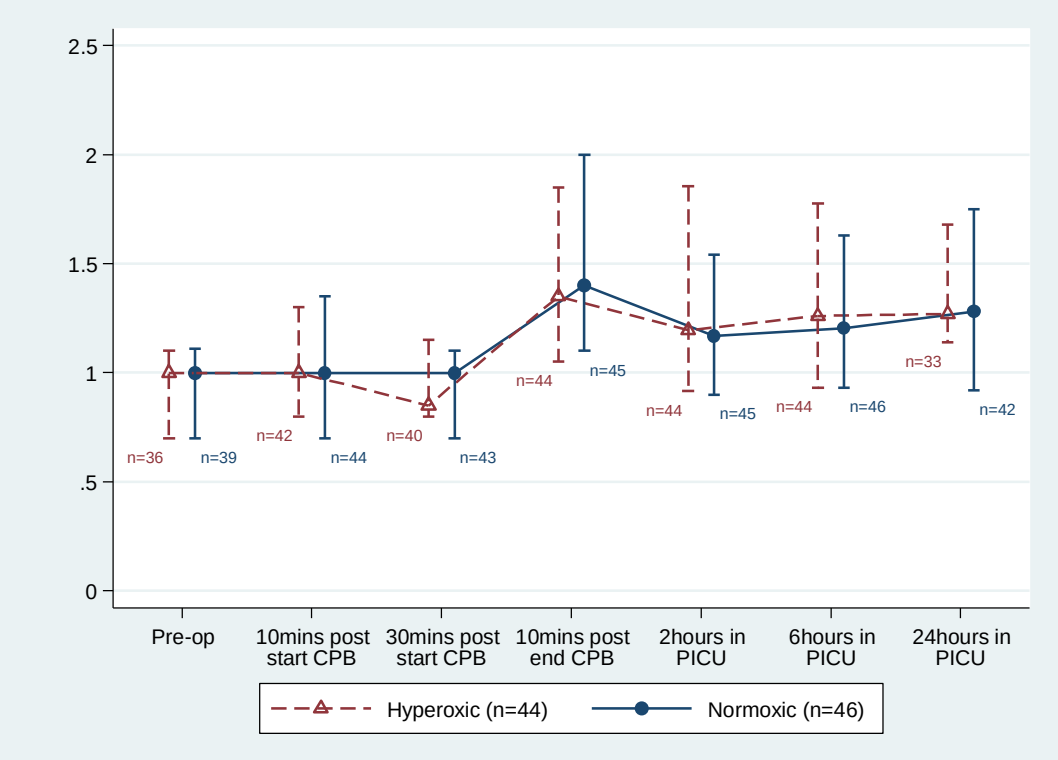


Figure 7 cBase levels over time

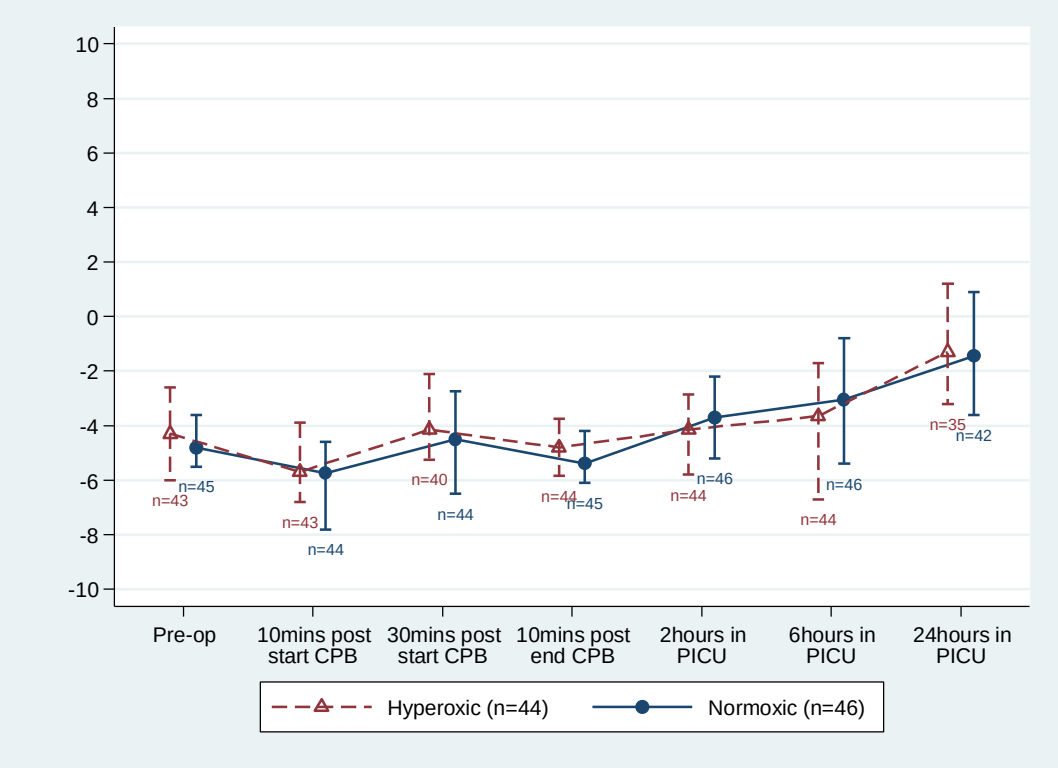


Figure 8 SO2 levels over time

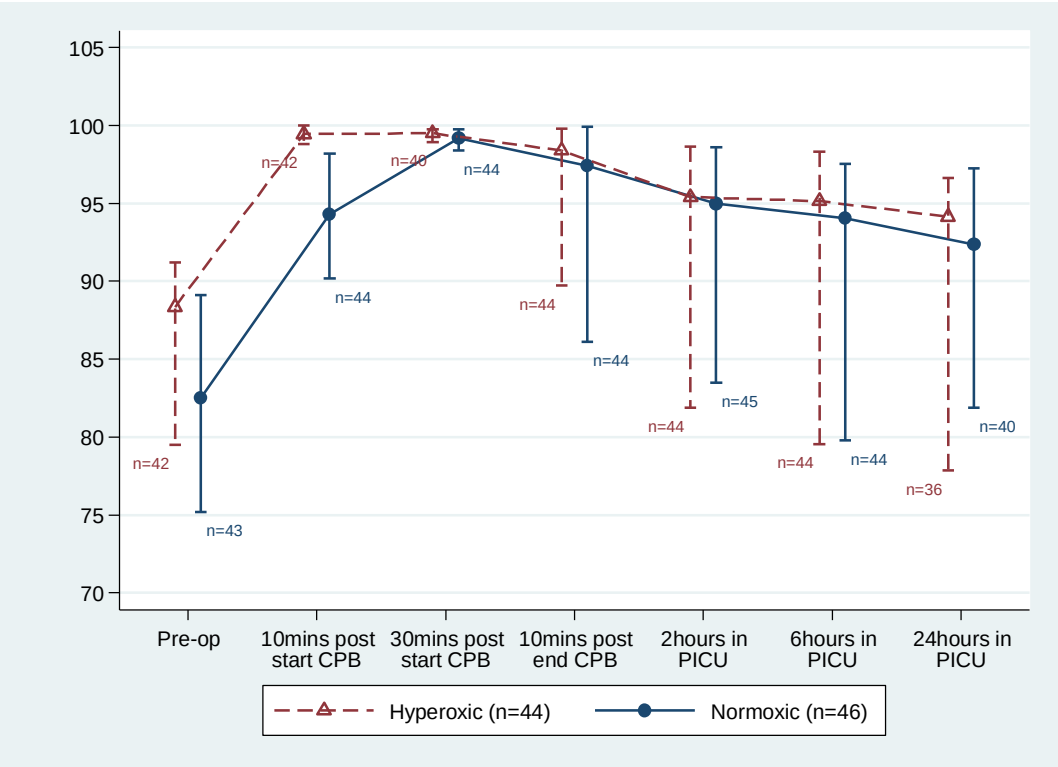


Figure 9 Glucose levels over time

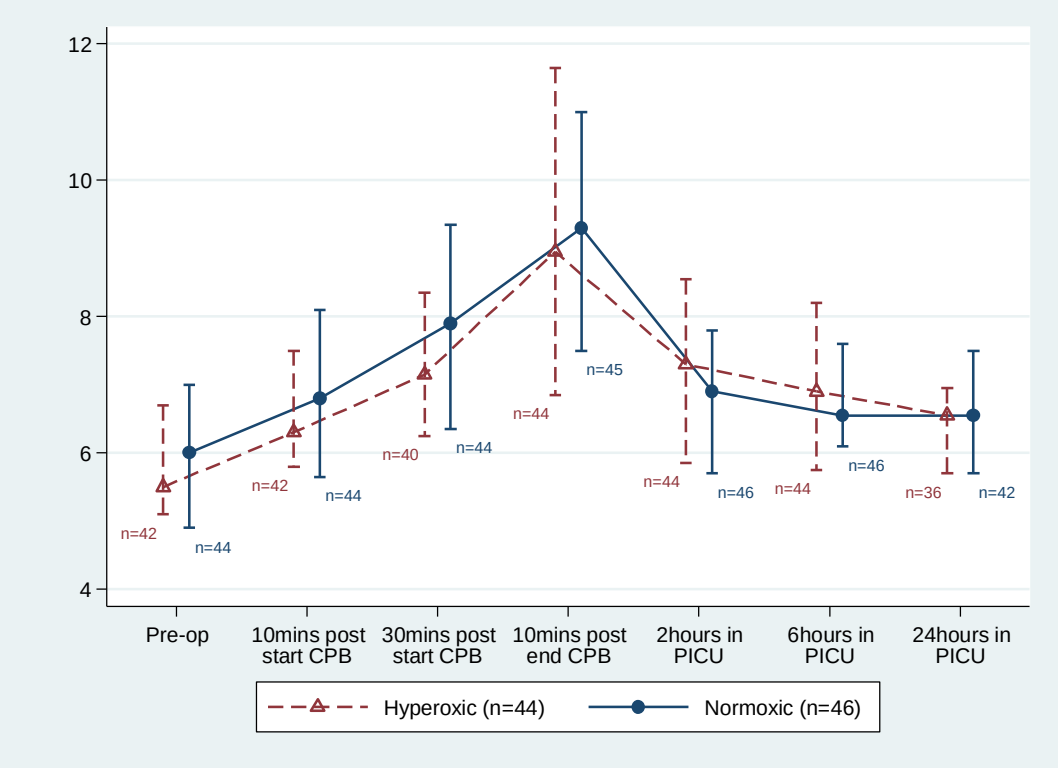
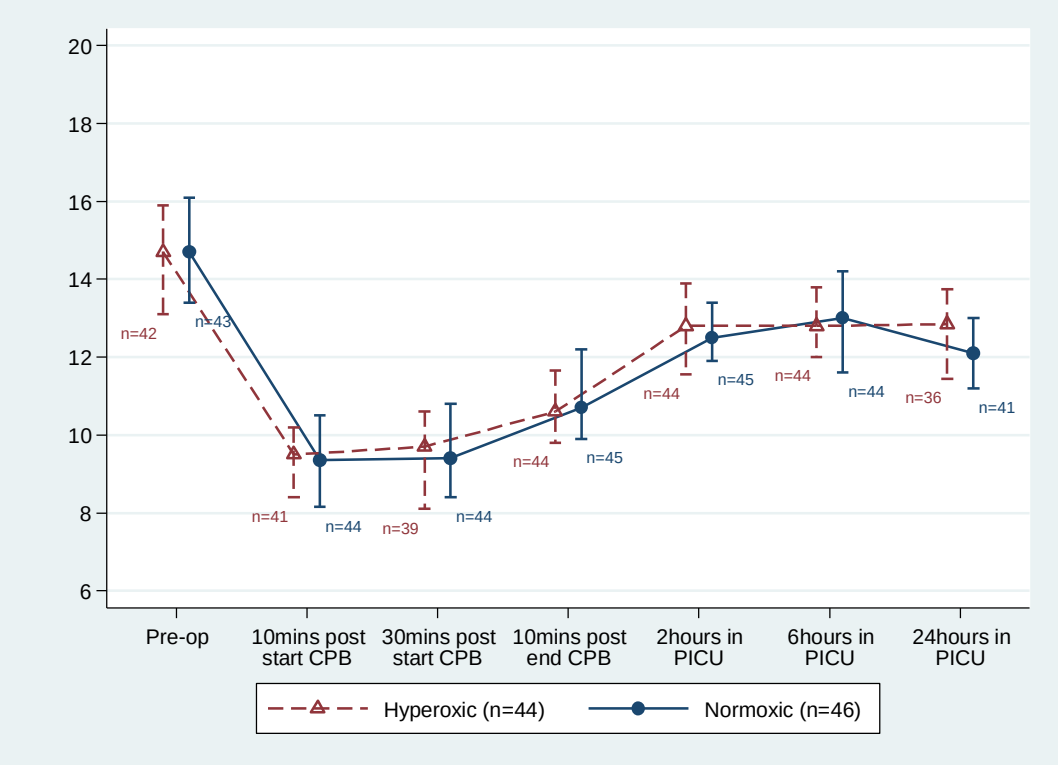


Figure 10 Haemoglobin levels over time



3.9.2 Developmental assessment using the Bayley Scales of Infant Development

This outcome is yet to be analysed.

3.9.3 Renal function

Renal function as measured by urea nitrogen and creatinine levels over the first 5 days post operation, by group, is shown in Figures 11 and 12. For both these measures, there were changes over time but no clear pattern distinguishing the two groups.

Figure 11 Creatinine levels over time

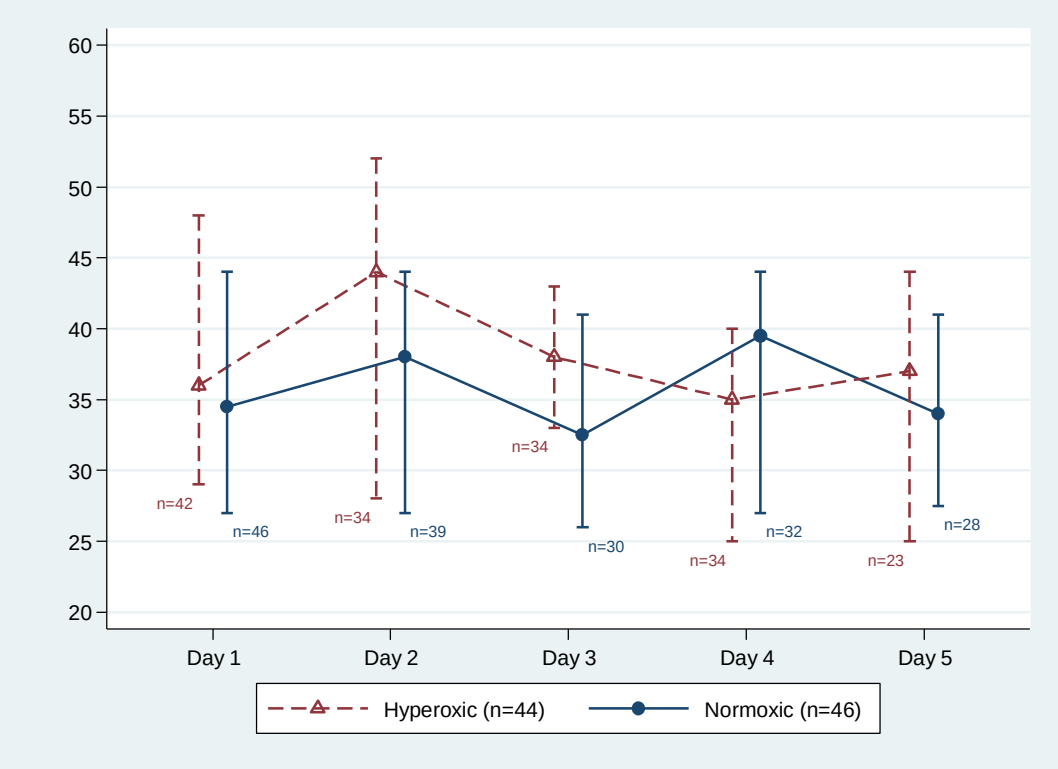
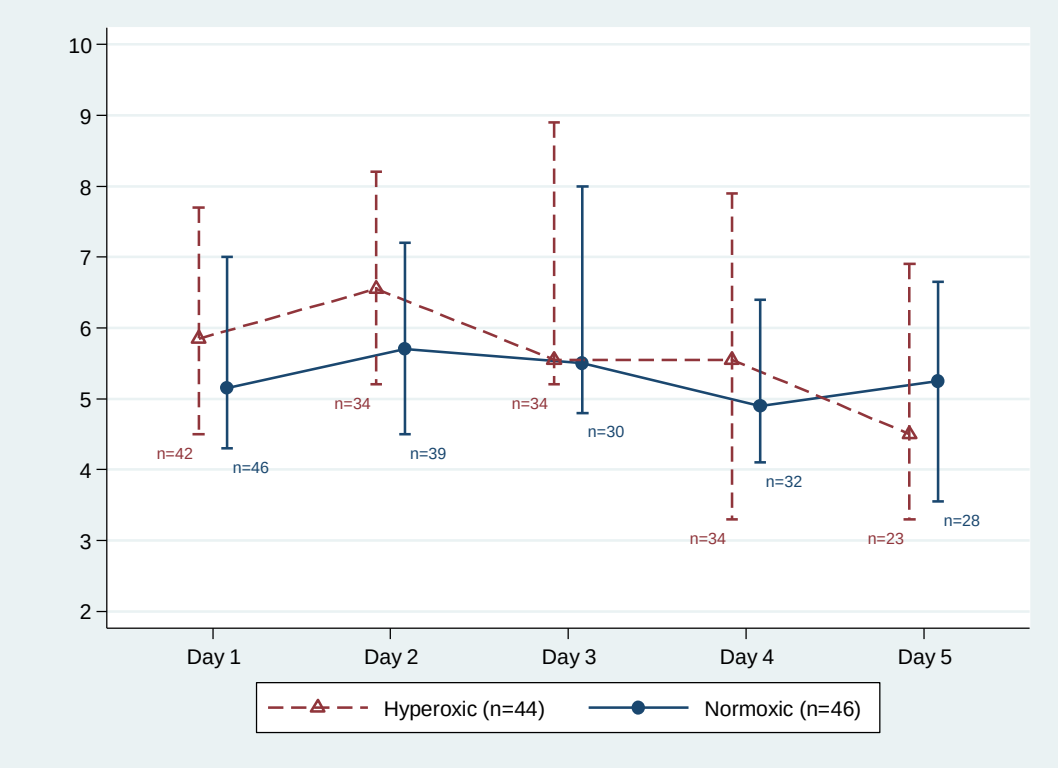


Figure 11 Urea levels over time



3.9.4 Gene expression and cell contractility associated with reoxygenation injury to the heart muscle

The gene expression results have been reported separately [21]. The samples obtained were inadequate for analysis of cell contractility.

3.10 Adverse events and postoperative complications

3.10.1 Adverse events by intention to treat

Three patients died following surgery, two in the normoxic group and one in the hyperoxic group. A total of 49 post-operative adverse events expected after cardiac surgery were observed; 27 (59%) Ain the normoxic group and 22 (50%) in the hyperoxic group (see Table 7). Most events occurred with similar frequency in the two groups; the only exceptions were renal complications which more common in the hyperoxic group (7% versus 0%) and bleeding complications which were more common in the normoxic group (9% versus 0%). Twelve patients experienced one or more complications which were classified as serious (2 in the hyperoxic group, 10 in the normoxic

group). The "serious" adverse events (normoxic, hyperoxic) were pacing (1, 1), pulmonary (3, 2), GI (1, 0), neurological (2, 1), bleeding (2, 0), infective (4, 1) and wound (1, 0) complications. However, it is important to note that the seriousness of the complication was not collected at the start of the trial. These data were added to the study CRFs part way through the trial and were only available for 37 participants.

Table 7 Adverse events by allocation

	Randomised to Hyperoxic (n=44)		Randomised to Normoxic (n=46)		Overall (n=90)	
	n	%	n	%	n	%
Expected adverse events pre-discharge	22/44	50.0%	27/46	58.7%	49/90	54.4%
Patient died	1/44	2.3%	2/46	4.3%	3/90	3.3%
Arrhythmia in PICU	11/44	25.0%	10/46	21.7%	21/90	23.3%
Peri-operative MI	0/44	0.0%	0/46	0.0%	0/90	0.0%
Post-operative cardiac arrest	1/44	2.3%	1/46	2.2%	2/90	2.2%
Post-operative pacing	8/44	18.2%	7/46	15.2%	15/90	16.7%
Haemodynamic support	2/44	4.5%	0/46	0.0%	2/90	2.2%
Pericardial effusion	0/44	0.0%	1/46	2.2%	1/90	1.1%
Pulmonary complications	10/44	22.7%	11/46	23.9%	21/90	23.3%
Renal complications	3/44	6.8%	0/46	0.0%	3/90	3.3%
GI complications	1/44	2.3%	1/46	2.2%	2/90	2.2%
Neurological complications	3/44	6.8%	2/46	4.3%	5/90	5.6%
Bleeding complications	0/44	0.0%	4/46	8.7%	4/90	4.4%
Infective complications	10/44	22.7%	12/46	26.1%	22/90	24.4%
Wound complications	1/44	2.3%	2/46	4.3%	3/90	3.3%
Expected SAEs pre-discharge *	2/18	11.1%	10/19	52.6%	12/37	32.4%
Unexpected SAEs pre-discharge **	3/44	6.8%	5/46	10.9%	8/90	8.9%
Unexpected SAEs post-discharge **	3/44	6.8%	11/46	23.9%	14/90	15.6%

Additionally, there were 22 unexpected serious adverse events reported in 17 children. Eight events were prior to hospital discharge (this included the 3 deaths) and 14 events were in the period from discharge to one year. All pre-discharge events prolonged the hospital stay and all post-discharge events resulted in hospitalisation. There were 16 unexpected serious adverse events in the normoxic group and 6 in the hyperoxic group. Twelve events were classified as severe, 2

moderate and 8 mild. Details of these events are given in Table 8. **It is important to note some 12 months reports requests from participants GP are still awaited.**

Table 8 Unexpected serious adverse events

Allocation	ID	Event	Timing	Max intensity	Outcome
Normoxic	1	Suspected Transient Ischaemic Attack (TIA)	Post discharge	Severe	Resolved, no sequelae
Normoxic	2	Pericardial effusion and sternal wound infection	Post discharge	Severe	Resolved, no sequelae
Normoxic	3	Probable viral infection	Post discharge	Mild	Resolved, no sequelae
Hyperoxic	4	Multiple complications	Pre discharge	Severe	Resolved, no sequelae
Hyperoxic	5	Reflux Oesophagitis	Post discharge	Severe	Resolved, no sequelae
Normoxic	6	Chylothorax, haematoma and haemothorax subsequent to pleural and pericardial effusions.	Post discharge	Moderate	Resolved, no sequelae
Normoxic (received hyperoxic)	7	Cyanotic spells, thrombocytosis, poor feeding	Post discharge	Severe	Resolved, no sequelae
Normoxic	8	Gastrojejumostomy tube blockage	Post discharge	Mild	Resolved, no sequelae
Normoxic	8	Readmission to PICU due to hypotension and hypoxia	Pre discharge	Severe	Resolved, no sequelae
Normoxic	8	Suspected tonsilitis and gastrostomy site infection	Post discharge	Mild	Resolved, no sequelae
Normoxic	8	High INR	Post discharge	Mild	Resolved, no sequelae
Normoxic (received hyperoxic)	9	Poor saturations, sepsis and increased inotropic requirement, leading to withdrawal of treatment and death	Pre discharge	Severe	Death
Normoxic	10	Minor head injury due to fall from bed	Post discharge	Mild	Resolved, no sequelae
Normoxic	11	Haemothorax	Pre discharge	Severe	Death

Allocation	ID	Event	Timing	Max intensity	Outcome
Hyperoxic	12	Insertion of Gastrostomy tube	Post discharge	Mild	Resolved, no sequelae
Hyperoxic	12	Diagnosed with Bilateral Pleural Effusions	Post discharge	Mild	Resolved, no sequelae
Hyperoxic	13	Multiple post-surgery complications resulting in death	Pre discharge	Severe	Death
Normoxic	14	Bacterial tonsillitis	Post discharge	Moderate	Resolved, no sequelae
Normoxic (received hyperoxic)	15	Gastroenteritis	Post discharge	Severe	Resolved, no sequelae
Hyperoxic	16	Poor weight gain preventing discharge from hospital	Pre discharge	Mild	Resolved, no sequelae
Normoxic	17	Irritable, crying and whimpering on withdrawing from Clonidine, examined by a neurologist.	Pre discharge	Severe	Resolved, with sequelae
Normoxic	17	Vomiting and not tolerating feeding	Pre discharge	Severe	Resolved, with sequelae

3.10.2 Adverse events treatment received

Six participants allocated to the normoxic group crossed over and received hyperoxic CPB (see Table 1). Examining adverse events by treatment received rather than treatment allocated resulted in 50 participants in the hyperoxic group compared to 40 in the normoxic group. The numbers experiencing any complication was similar (27/50, 54% versus 22/40, 55%). There were some changes in the frequency of some individual complications, but the rates remained similar between the two groups (see Table 10 for details). Of the 12 patients who experienced one or more complications classified as serious 9 received the controlled oxygen (normoxic). The "serious" adverse events (received normoxic, hyperoxic) were pacing (1, 1), pulmonary (3, 2), GI (1, 0), neurological (2, 1), bleeding (2, 0), infective (3, 2) and wound (1, 0) complications.

Table 9 Adverse events by treatment received

	Received Hyperoxic (n=50)		Received Normoxic (n=40)		Overall (n=90)	
	n	**%**	**n**	**%**	**n**	**%**
Expected adverse events pre-discharge	27/50	54.0%	22/40	55.0%	49/90	54.4%
Arrhythmia in PICU	12/50	24.0%	9/40	22.5%	21/90	23.3%
Peri-operative MI	0/50	0.0%	0/40	0.0%	0/90	0.0%
Post-operative cardiac arrest	1/50	2.0%	1/40	2.5%	2/90	2.2%
Post-operative pacing	9/50	18.0%	6/40	15.0%	15/90	16.7%
Haemodynamic support	2/50	4.0%	0/40	0.0%	2/90	2.2%
Pericardial effusion	0/50	0.0%	1/40	2.5%	1/90	1.1%
Pulmonary complications	11/50	22.0%	10/40	25.0%	21/90	23.3%
Renal complications	3/50	6.0%	0/40	0.0%	3/90	3.3%
GI complications	1/50	2.0%	1/40	2.5%	2/90	2.2%
Neurological complications	3/50	6.0%	2/40	5.0%	5/90	5.6%
Bleeding complications	1/50	2.0%	3/40	7.5%	4/90	4.4%
Infective complications	13/50	26.0%	9/40	22.5%	22/90	24.4%
Wound complications	1/50	2.0%	2/40	5.0%	3/90	3.3%

4. Discussion

To follow when the formal comparative analyses have been completed.

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