Ethnicity and Observed Oxygen Saturations, Fraction of Inspired Oxygen and Clinical Outcomes: A Post-Hoc Analysis of the Oxy-PICU trial of Conservative Oxygenation.

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Abstract (289 words)

Objectives: A conservative oxygenation strategy, targeting peripheral oxygen saturations (SpO_2) between 88-92% in mechanically ventilated children on PICU, was associated with a shorter duration of organ support and greater survival compared to SpO_2 >94% in our recent

Oxy-PICU trial. SpO_2 monitors may overestimate arterial oxygen saturation (SaO_2) in patients with higher levels of skin pigmentation compared to those with less skin pigmentation. We investigated if ethnicity was associated with changes in distributions of SpO_2 and FiO_2 and outcome.

Design: Post-hoc analysis of a pragmatic, open-label, multi-centre randomised controlled trial.

Setting: Fifteen PICUs across England and Scotland.

Patients: Children aged 38 weeks corrected gestational age to 15 years accepted to a participating PICU as an unplanned admission and receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange.

Methods: Hierarchical regression models for SpO_2 and fraction of inspired oxygen (FiO_2), and ordinal models for the primary trial outcome of a composite of duration of organ support at 30 days and death, were used to examine the effects of ethnicity, accounting for baseline SpO_2, FiO_2 and mean airway pressure and trial allocation.

Measurements and Main Results: Ethnicity data were available for 1577 of 1986 eligible children, 1408 (89.3%) of which were White, Asian or Black. SpO_2 and FiO_2 distributions did not vary according to Black or Asian ethnicity compared to White children. The trial primary outcome measure also did not vary significantly with ethnicity. The point estimate for the treatment effect of conservative oxygenation in Black children was 0.64 (95% confidence interval 0.33 to 1.25) compared to 0.84 (0.68-1.00) in the overall trial population.

Conclusions: These data do not suggest a modification by ethnicity of the association between improved outcomes and conservative oxygenation strategy in mechanically ventilated children on PICU.

Introduction

Recent data suggest that peripheral oxygen saturation (SpO_2) monitors may less accurately reflect the arterial oxygen saturation (SaO_2) in Black patients or patients with higher levels of skin pigmentation compared to those with less skin pigmentation.(1–4) Recent systematic reviews and meta-analyses describe the risk of overestimating SaO_2 in patients with high levels of skin pigmentation or identified as Black or African-American, leading to under-recognition and delay to treatment of clinically significant hypoxaemia.(4, 5)

In the Oxy-PICU trial, evaluating conservative oxygenation, we reported that an SpO_2 target of 88-92% offers a small clinical benefit over liberal oxygenation targets (usual care of SpO_2 >94%).(6) These oxygenation targets were solely based on SpO_2 readings, therefore there was a possibility of a heterogeneity of treatment effect by levels of skin pigmentation.

We conducted a post-hoc analysis of Oxy-PICU trial data to test the null hypothesis that ethnicity has no effect on the distributions of SpO_2 and fraction of inspired oxygen (FiO_2) or on the effect of the intervention on the trial primary outcome measure of a ranked composite of days of organ support and mortality.

Methods

The protocol for the Oxy-PICU trial has been published previously(7) with prespecified analysis of clinical and cost effectiveness.(6) Between September 2020 and May 2022, 2040 emergency admissions to UK paediatric intensive care units (PICU) who were receiving invasive ventilation and supplemental oxygen were randomised 1:1 to a conservative SpO_2 target of 88-92% or usual care (SpO_2 >94%). The protocol had research ethics approval (19/EE/0362) and was registered (ISRCTN92103439) prior to recruitment.

In addition to baseline data, SpO_2, FiO_2 and mean airway pressure (Pmean) were collected hourly in the first 7 days of invasive mechanical support and 12-hourly thereafter. The primary

outcome was duration of organ support up to day 30 or death as ordinal rank from 1-31 (with death ranked as the worst outcome).

A statistical analysis plan for this post-hoc analysis was prepared prior to data analysis (supplemental appendix).

Ethnicity is a pre-existing field in the United Kingdom Paediatric Intensive Care Audit Network (PICANet) registry and was categorised as White, Black, Asian, Mixed, Other or Unknown prior to analysis. Children classified as ‘Mixed’, ‘Other’ or ‘Unknown’ were excluded from the analysis because no association to skin melanin content could be inferred. All cases were included in a sensitivity analysis (supplementary eFigure 1).

Three regression models were constructed to explore the covariates that contributed to the distributions of A) SpO_2 and B) FiO_2 and C) the primary outcome of duration of organ support or death. SpO_2 and FiO_2 distributions were examined using hierarchical mixed effects models. We included two random effects at the nested levels of recruitment site and patient, to account for heterogeneity between sites and patients. SpO_2 and FiO_2 were interpreted as continuous and modelled with a linear regression. The SpO_2 model accounted for FiO_2 at the time of SpO_2 measurement and baseline SpO_2. The FiO_2 model accounts for SpO_2 and Pmean at the time of FiO_2 measurement and baseline FiO_2, SpO_2 and Pmean. Both models included trial group allocation (conservative or liberal oxygenation targets) and ethnicity.

The clinical outcome measure of days of organ support or death is a composite ordinal outcome. As there are no repeated measurements for this variable, we analysed this with an ordered logistic regression, adding a random effect for recruitment site. The model accounted for baseline severity (Paediatric Index of Mortality, PIM-3), age on admission, baseline SpO_2 and trial group allocation.

All models include an interaction term between ethnicity and the expected main explanatory variable to explore ethnicity as an effect modifier. For SpO_2 and the clinical outcome we

include a factor term of treatment allocation and ethnicity, while for the FiO_2 outcome we include the factor between ethnicity and corresponding SpO_2 measurement.

We planned to investigate the relationship of PaO_2 and SpO_2 with non-linear regression.

Full details can be found in the statistical analysis plan in the supplementary material which was written prior to the analysis.

Analysis was performed in R version 4.3.0. Using the “lme4” and “ordinal” packages for the linear (lmer) and ordered logistic regression models (clmm2). (8, 9)The full implementation can be found on GitHub (https://github.com/Martin-Wiegand/Pulsoxy-projects.git).

Missing data at baseline was imputed by the next closest measurement to baseline, up to 6 hours after randomisation. Repeated measurements were analysed by complete case analysis, and time points were omitted if any of the necessary covariates were missing. As a sensitivity analysis, we generated a model with 40 imputed data sets combined via Rubin’s rules, which did not indicate that missing data significantly impacted the findings of the models (supplementary eFigure 2).

Results

Of 2040 patients randomised, consent for the collection for the trial primary outcome was available in 1986.(6) Of these 578 had ‘Mixed’, ‘Other’ or ‘Unknown’ ethnicity recorded and were hence excluded from the current study (Figure 1). Of the 1408 remaining patients, 1066 were White, 117 Black and 225 Asian. Baseline characteristics are presented in Supplemental Table 1 and were representative of the full trial population and typical of the UK PICU population meeting these inclusions.(6) Missing data meant that the final SpO_2 analysis (A) included 114,887 data points, FiO_2 analysis (B) 47,814 data points and the clinical outcome of organ support or death (C) 1352 patients (Figure 1).

As expected, allocation to the conservative oxygenation arm was associated with a reduction in both the observed SpO_2 levels and FiO_2 administered. Black or Asian ethnicity did not modify the observed values of SpO_2 or FiO_2 administered compared to White children. (Figure 2 A and B).

The main trial primary outcome measure (ranked composite of days of organ support and mortality) was reduced by allocation to the conservative oxygenation group. In the subset of patients analysed here, the point estimate is similar to the full trial results, but the confidence interval crosses one. This likely reflects the reduced sample size in this analysis. Neither Asian nor Black ethnicity was associated with a significant difference in outcome, nor a significant modification of the effect of conservative oxygenation. However, the point estimates of odds ratios for outcome with Black ethnicity suggest that such patients tend towards spending longer in organ failure or dying more frequently on PICU. (Figure 2C) This effect is not visible when combined with the trial group allocation, indeed the point estimate tends towards greater benefit of conservative oxygenation in Black patients. (Figure 2C). Sensitivity analysis with all ‘Mixed’, ‘Other’ and ‘Unknown’ cases included did not significantly alter these results (supplementary eFigure 1)

The planned investigation of relationship of PaO_2 and SpO_2 with non-linear regression was limited by low numbers of PaO_2 values and inexact time-pairing of measurements with SpO_2 observations (supplementary eFigure 6).

Discussion

In a post-hoc analysis of the Oxy-PICU trial, we found no significant effects of ethnicity on observed SpO_2 values, FiO_2 administered nor the primary clinical outcome of days of organ support or death.

Given the reported overestimation of SaO_2 values in pigmented skin especially at lower true values,(5) we would have anticipated FiO_2 values might be somewhat lower in the Black population (in response to falsely high SpO_2 readings). Perhaps more importantly, Black patients might have been exposed to lower SaO_2 values e.g. below 88% when we were targeting SpO_2 88-92%. While we found no evidence of this, since we did not have data on SaO_2, we cannot exclude truly lower SaO_2 values in this population. Black children tended to have worse clinical outcomes than White patients. Similar observations have been made in other UK datasets.(10, 11) Interestingly however, Black children gained at least as much benefit from conservative oxygenation as other ethnicities. Indeed, the point estimate for regression coefficient with conservative oxygenation amongst Black children was 0.64 compared to 0.84 in the overall population. This effect was not significant but does raise the possibility that the true nadir of risk for a conservative oxygenation strategy is lower than an SaO_2 of 88%.

The only other multiple center randomised trial of a conservative oxygenation strategy in children, the COAST trial in children with pneumonia in East Africa, was stopped early because of recruitment challenges.(12) While this was in a very different healthcare system without access to intensive care, the point estimate for mortality in this Black population also slightly favoured a strategy of not starting supplemental oxygen unless the SpO_2 fell below 80%.

Our study has several weaknesses. The sample size was lower than the original trial, which itself was only just adequately powered. The ethnicity classification was limited. Skin tone and melanin content are highly variable within the broad categories used, this may have diluted the observed effects. The majority of children of 'Asian' ethnicity in the United Kingdom have an Indian sub-continental heritage rather than east, or south-east, Asian.

Despite these limitations, we have demonstrated that the outcome from the Oxy-PICU trial does not vary significantly with the ethnicity of our patients. The small benefits of the trial should therefore be available to all patients, and the SpO_2 target of 88-92% is safe across ethnic groups. The optimal target for conservative oxygen remains unknown.

Contributions

MP, SR, and GALJ conceived, and designed this secondary analysis with MW, DWG, KMR, DAH and PRM. KT, EG, and DAH directly accessed and verified the data and MW conducted the analyses. MP, SR, MW and GALJ drafted the manuscript. All authors critically revised and approved the manuscript for submission.

Conflicts of interest

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Figures.

Figure 1. Flow chart of patients and observations included in the post-hoc analysis of the relationship between ethnicity and SpO_2, FiO_2 and the Composite Primary Outcome Measure of Days of Organ Support up to day 30 or death in the Oxy-PICU trial.

Figure 2 The relationship between of ethnicity and trial group allocation and SpO_2, FiO_2, and the Composite Primary Outcome Measure of Days of Organ Support up to day 30 or death in the Oxy-PICU trial.

A) Forest plot of model coefficients of the hierarchical linear regression of repeated SpO_2 measurements.

B) Forest plot of model coefficients of the hierarchical linear regression for repeated FiO_2 measurements.

C) Forest plot of model coefficients for the hierarchical ordinal logistic regression model, for the composite outcome of organ support days and 30 day mortality.

Figure 1

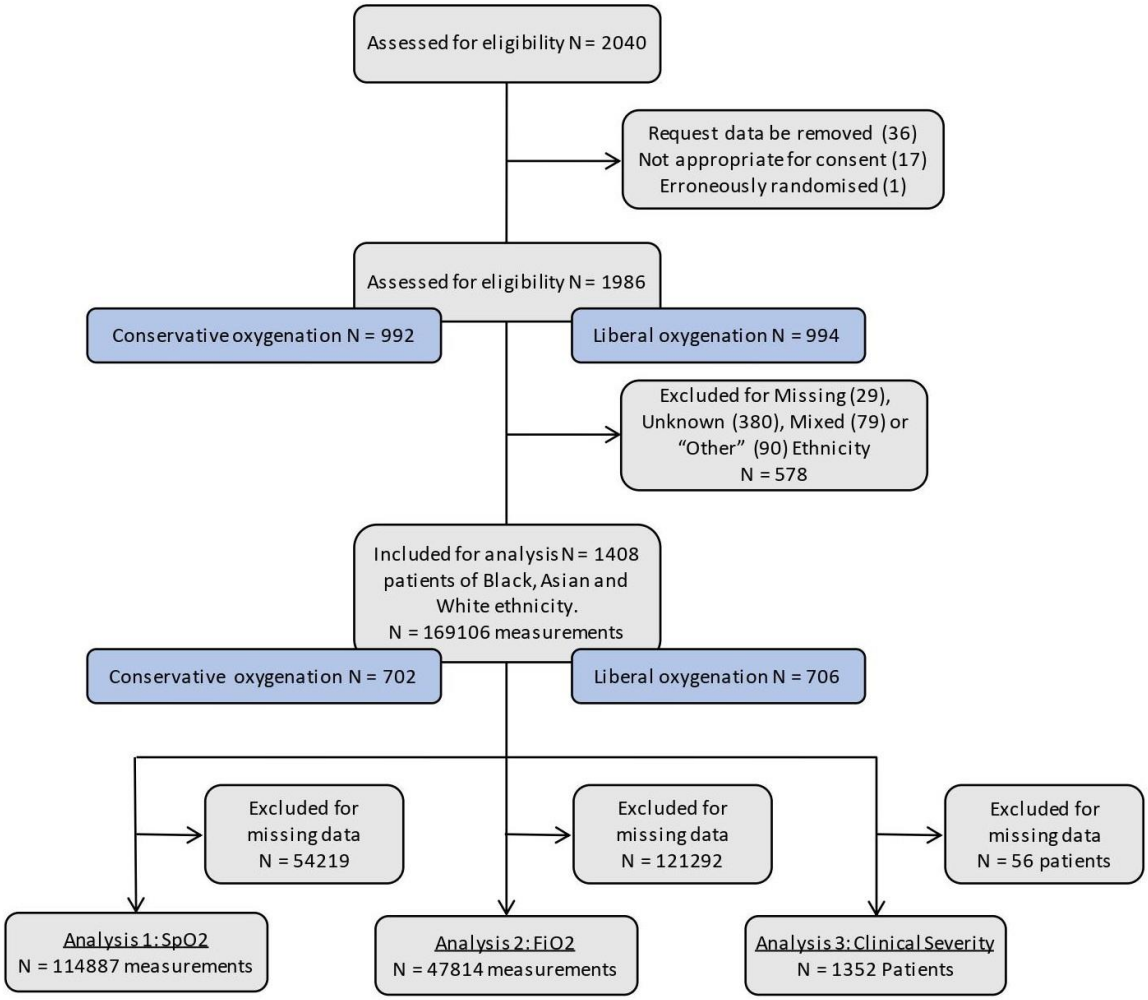
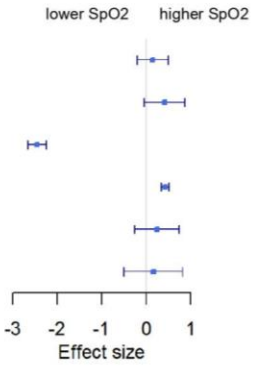

Assessed for eligibility N = 2040
Request data be removed (36)
Not appropriate for consent (17)
Erroneously randomised (1)
Assessed for eligibility N = 1986
Conservative oxygenation N = 992
Liberal oxygenation N = 994
Excluded for Missing (29), Unknown (380), Mixed (79) or "Other" (90) Ethnicity N = 578
Included for analysis N = 1408 patients of Black, Asian and White ethnicity. N = 169106 measurements
Conservative oxygenation N = 702
Liberal oxygenation N = 706
Excluded for missing data N = 54219
Excluded for missing data N = 121292
Excluded for missing data N = 56 patients
Analysis 1: SpO2 N = 114887 measurements
Analysis 2: FiO2 N = 47814 measurements
Analysis 3: Clinical Severity N = 1352 Patients

Figure 2

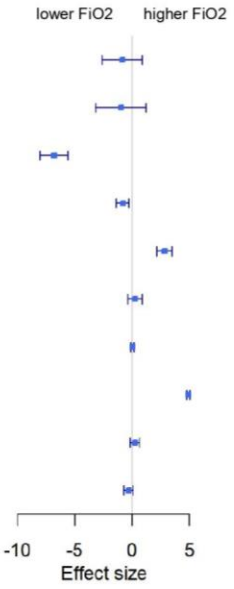
A) Hierarchical model coefficients for SpO2 outcome

Covariate	Estimate	Lower	Upper
Asian	0.14	-0.21	0.49
Black	0.41	-0.054	0.87
Conservative treatment	-2.5	-2.7	-2.3
Baseline SpO2 (standardised)	0.42	0.33	0.51
Conservative treatment * Asian	0.24	-0.26	0.73
Conservative treatment * Black	0.16	-0.5	0.82



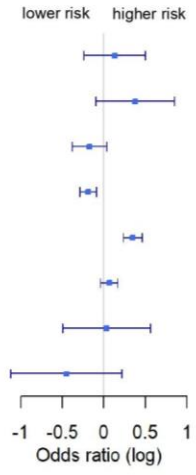
B) Hierarchical model coefficients for FiO2 outcome

Covariate	Estimate	Lower	Upper
Asian	-0.84	-2.6	0.92
Black	-0.94	-3.1	1.3
Conservative treatment	-6.8	-8	-5.6
Baseline SpO2 (standardised)	-0.8	-1.3	-0.26
Baseline FiO2 (standardised)	2.8	2.2	3.5
Baseline Pmean (standardised)	0.26	-0.37	0.89
SpO2 (standardised)	0.046	-0.12	0.21
Pmean (standardised)	4.9	4.7	5.1
SpO2 (standardised) * Asian	0.26	-0.14	0.67
SpO2 (standardised) * Black	-0.29	-0.69	0.098



C) Ordinal regression coefficients for combined mortality and organ support

Covariate	Estimate	Lower	Upper
Asian	0.131	-0.238	0.501
Black	0.377	-0.093	0.847
Conservative treatment	-0.172	-0.386	0.042
Baseline SpO2 (standardised)	-0.185	-0.284	-0.086
PIM-3 score (standardised)	0.351	0.24	0.461
Age (standardised)	0.066	-0.037	0.169
Conservative treatment * Asian	0.033	-0.494	0.561
Conservative treatment * Black	-0.451	-1.12	0.219



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