

Admission partial pressure of oxygen and mortality in critically ill children: A cohort study and systematic review

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Abstract

Objective:

To describe the relationship between arterial oxygen tension (PaO₂) at intensive care admission and mortality in critically ill children and to review systematically the literature describing this relationship.

Methods

Cohort Study

A review of consecutive tertiary paediatric intensive care (PIC) admissions (January 2004-December 2014) in a single center. The relationship between admission PaO₂, crude and standardized mortality was explored using non-linear regression.

Systematic Review

A search of MEDLINE (1950 - Jan 2015), EMBASE (1980 - Jan 2015), Cochrane and DARE databases was undertaken using the terms: 'hyperoxia', 'hypoxia', 'critically ill children', 'paediatric intensive care', 'mortality' and/or 'survival'.

Randomised control trials or cohort studies describing the effect of hyperoxia or hypoxia on mortality in patients <18 years of age were included. The association of hyperoxia [arterial oxygen tension (PaO₂) >300 torr (40 kPa)] and hypoxia [PaO₂ <60 torr (8 kPa) or peripheral oxygen saturations < 90%] to mortality in critically ill children was explored.

Results:

Cohort study: Of 14,321 admissions, 7410 children had recorded PaO₂ and FiO₂ at admission. Crude mortality was 7.4% (555/7410). This varied with admission PaO₂ from 15.4% (204/1324) in the hypoxia group (<8kPa) to 5.3% (287/5385) with normoxia and 9.1% (64/701) in the hyperoxic group (>40kPa). Non-linear regression displayed a 'U-shaped' relationship between PaO₂ and crude and case-mix adjusted mortality.

Systematic review: 14 studies and one conference abstract were eligible for inclusion. Eleven studies (n=5280) relate to hypoxia with combined odds ratio (OR) for death, of 3.13 (95%CI: 1.79-5.48, p < 0.001) compared to normoxia. Six studies (n=2012) relate to hyperoxia and suggest no effect on mortality compared to normoxia: OR 1.15 (95%CI: 0.42-3.17, p = 0.77).

Conclusions:

Hypoxia at admission is associated with increased mortality in critically ill children, whilst the association with hyperoxia is less clear. The cohort study demonstrated a 'U-shaped' association between admission PaO₂ and mortality. Further examination is needed to explore the effect of hyperoxia upon mortality prediction accuracy.

Introduction

Associations between hypoxia and poor outcome are well known.(1, 2) However the risks of hypoxia vary widely with context and time-frame.(3, 4) *Hyperoxia* is associated with increased mortality following stroke, cardiac arrest and traumatic brain injury in critically ill adults.(5-7)

The true distribution of risk associated with levels of oxygenation during critical illness is likely to be complex. De Jonge reported a U-shaped relationship between early PaO₂ and mortality in adult intensive care units.(8) Martin and Grocott proposed '*precise control of arterial oxygenation*' and '*permissive hypoxaemia*' for optimising risk and benefit of oxygen therapy during critical illness.(9) Avoidance of hyperoxia was safe in a randomized pilot trial of mechanical ventilated adults comparing conservative (88-92%) and liberal (>96%) oxygen saturation targets.(10) In infants with bronchiolitis, oxygen saturation targets of >90% were as safe as >94%, and required shorter durations of support.(11)

There is no consensus on the ideal arterial oxygen tension in critically ill children. Here we examine the hypothesis that the partial pressure of oxygen (PaO₂) at admission does not influence risk-adjusted mortality in critically ill children in a large cohort and through systematic review of the literature.

Methods

Cohort study

We reviewed prospectively collected data for all admissions to the pediatric, neonatal and cardiac critical care units at Great Ormond Street Hospital (GOSH) over an 11-year period (Jan 2004- Dec 2014).

Patients were included if they had a documented PaO₂ and FiO₂ at admission. The definitions of normoxia, hypoxia, hyperoxia and admission PaO₂ reflect those used by Kilgannon and De Jonge.(9, 13)

The Paediatric index of Mortality 2 score was recorded and a modified score (mPIM) was calculated for each patient by excluding the coefficient of FiO₂ /PaO₂ (F/P ratio) from the logit equation. Patients were empirically categorised into 6 groups according to their admission PaO₂ (<8, 8.1-10, 10.1-13, 13.1-25, 25.1-40 and >40kPa). Standardised mortality ratio (SMR), modified SMR (mSMR, calculated using mPIM) and 95% confidence intervals were calculated and plotted for each group using PIM2 and mPIM.

Regression curve estimation (SPSS, IBM Software v21.0) was used to determine best-fit model for the PaO₂ – mortality relationship.(13) Non-linear regression analysis with mortality as the outcome and admission PaO₂, age, ethnicity, weight and mPIM2 as co-variates was performed to assess the relationship between oxygenation and crude and case-mix adjusted mortality.

Systematic review

The systematic review was performed following the ‘Preferred Reporting Items for Systematic reviews and Meta-Analyses’ (PRISMA) guidelines.(14) The inclusion criteria were:

- Age - 4 weeks - 18 years
- For the observation cohort, hyperoxia defined as PaO₂ >300 torr (40 kPa) or hypoxia defined as peripheral oxygen saturations <90% or PaO₂ <60 torr (8 kPa).

- For the comparison cohort, normoxia defined as PaO₂ between 60-300 torr (8.1-40 kPa) or peripheral oxygen saturations >90%. Alternative thresholds were analysed separately. (Supplemental digital content 1)
- Randomised control trials (RCT) or cohort studies
- Outcome measure - Mortality at hospital discharge.

Search strategy:

The terms 'hyperoxia', 'hypoxia', 'survival' and 'critically ill children' or 'pediatric intensive care' and 'mortality' (supplemental digital content 2-4) were used to identify RCTs and cohort studies in Medline (1950-Jan2015), EMBASE (1980-Jan2015), Cochrane and DARE databases. The search was conducted in April 2015.

Primary summary measure and meta-analysis:

A meta-analysis was performed with OpenMeta[Analyst] software. I² was used as the measure of consistency for heterogeneity analysis. For subgroup analysis, the studies were divided into patients admitted with lower respiratory tract infection (LRTI) or CA or TBI.

Results

Cohort study

Over the 11-year period, 7410 of 14,321 admissions had a recorded PaO₂ in the first hour. Of these, 1324 (17.8%) were hypoxic, 5385 (72.6%) were normoxic and 701 (9.4%) were hyperoxic on admission. The crude mortality was 204 (15.4%), 287 (5.3%) and 64 (9.1%) respectively. PaO₂ and crude mortality was found to have a quadratic (U-shaped) relationship using non-linear regression analysis with PaO₂, age, gender and mPIM as co-

variates. (Figure 1) The timing of death was described in KM curves. (Supplemental digital content – 5)

On the basis of the primary diagnosis on admission, the patients with cyanotic congenital heart disease were identified and separately analysed. The U-shaped relationship between PaO₂ and crude mortality was preserved even in this subgroup of children with cyanotic cardiac disorders. (Supplemental digital content - 6)

The standardized mortality ratio (SMR) and modified standardized mortality ratio (mSMR) were 0.93 and 1.34 for the hypoxic group (PaO₂ <8 kPa), 0.75 and 0.83 for the normoxic group (8-40 kPa) and 0.82 and 0.85 the hyperoxic group (>40 kPa). (Figure 2)

Systematic review

Study selection and characteristics

A single reviewer (SR) performed the search resulting in 1749 articles. Duplicate publications (155) were discarded. From the remaining 1594 articles, 1513 were excluded after abstract review. 81 articles were reviewed as full text, of which 66 were excluded as being of unsuitable study design. (Figure 3) No study investigated cyanotic congenital heart disease group.

The hypoxia studies analysed were: 4 cardiac arrest (CA) cohort studies, 3 LRTI, 2 post TBI and one each of children with malaria and diarrhoea. The hyperoxia studies analysed were: 5 CA cohort studies and 1 TBI study.

Hypoxia

The crude mortality in the hypoxic patients was 26.2% compared to 19.9% in the normoxia

group.

Eleven studies of 5280 children revealed a higher odds ratio of deaths with hypoxia compared to normoxia (OR-3.13, 95%CI: 1.79-5.48, $p < 0.001$). Heterogeneity was high ($I^2=86\%$). (Figure 4)

Hyperoxia:

The crude mortality from all the hyperoxia studies was 38.5% for the hyperoxia group and 38.4% in the normoxia group.

Six studies of 2012 children revealed no effect on mortality. The combined OR risk of death with hyperoxia compared to normoxia was 1.15 (95%CI: 0.42-3.17, $p = 0.77$). Heterogeneity was high ($I^2=82\%$). (Figure 4)

Subgroup analysis

The odds of death with hypoxia were higher in cardiac arrest, lower respiratory tract infection and traumatic brain injury subgroups. There was no association between hyperoxia and mortality in the CA subgroup. (Supplemental digital content – 7)

Tables 1-2 and supplemental digital content 8 and 9 (tables 3-4) give a summary of the characteristics recorded from the studies including the odds ratio and the outcome measures.

Risk of bias across studies:

The funnel plots of both hypoxia and hyperoxia studies suggest a publication bias. (Supplemental digital content – 10)

Discussion

Our cohort study demonstrates a quadratic (U-shaped) relationship between admission PaO₂ and mortality in critically ill children. As the PaO₂ increased the difference between SMR and mSMR ceased to exist. Thus, the influence of PaO₂ on PIM2 predicted risk of death is higher in the hypoxic range than the hyperoxic range. The systematic review indicates worse outcome with hypoxia compared to normoxia.

Hypoxia has a detrimental effect in critically ill children. This effect has been best described in the context of TBI.(16-17) Our findings support international recommendations on the management of TBI in children.(17)

The effect of hyperoxia on the outcome in various critically ill patient subgroups was recently reported.(7, 18) However, this relationship lacks widespread agreement. (19) There was no evidence of the increased mortality with hyperoxia in the overall population of critically ill children in our study. Of note, the odds of death with hyperoxia increased insignificantly in children admitted following cardiac arrest. This is consistent with the adult reports.(12)

The 'U-shaped' relationship between admission PaO₂ and mortality from our study differs from the inverse relationship between PaO₂ and mortality in the PIM2 model. There may be two explanations to this apparent dissimilarity. Although hyperoxic children seem to have a higher crude mortality, the relationship may not be causal. They are hyperoxic because clinicians recognise them as being sick and are reluctant to wean oxygen. Alternatively, PIM2 may need to have a modified coefficient for hypoxia and hyperoxia.

Limitations

The retrospective design and heterogeneous patient population with different mechanisms for hypoxia or hyperoxia make interpretation of the results difficult. We focused on the relationship between PaO₂ and mortality. While PaO₂ is a marker of alveolar gas exchange, tissue oxygen delivery is influenced by various factors, including haematocrit, macro and

microcirculatory parameters. The effect of ventilatory strategy on PaO₂ was not explored. We did not seek to investigate association between PaO₂ and attributed cause of death. We felt this analysis would be confounded by wide variability in practice in the recorded cause of death.

A more detailed analysis of the distribution and severity of organ failures with PaO₂ would be of interest and will be the subject of future work. However we would hypothesize that multi-organ failure would be present at both extremes – since organ dysfunction can be secondary to hypoxia or increased reactive oxygen species during hyperoxia. The picture is further complicated by the contribution from any iatrogenic injury from more aggressive treatments.

Finally we accept that the mode of death, and withdrawal of care due to ongoing hypoxia may introduce bias to our association. In the systematic review, the possibility of selection bias within each study is high. The funnel plots suggest some reporting bias.

Nearly all the studies explore the relationship of PaO₂ either less than 60 torr (8 kPa) or greater than 300 torr (40 kPa) on mortality suggesting an inherent bias in the setting up of PaO₂ thresholds for the cohorts. Most of the studies included in this review have small sample sizes (< 200 patients). This further limits the generalizability of the results. However, despite these limitations our study would inform future studies in this area.

Conclusions

Our systematic review suggests that avoiding hypoxia is beneficial in all critically ill children, particularly in the traumatic brain injury subgroup. Whether hyperoxia has an association with mortality is not clear. Thresholds for hyperoxia may have to differ depending on age, pre-ICU condition, and the disease process among other factors. Adequate oxygenation based on objective end organ perfusion indices may be more important than a single PaO₂ value on admission to ICU. The cohort study displays a 'U-shaped' admission PaO₂-mortality relationship that warrants further scrutiny.

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Figure legends

Figure 1 – PaO₂– Mortality

Relationship between arterial partial pressure of oxygen on admission and unadjusted mortality in 7410 critically ill children admitted to Great Ormond St Hospital Intensive Care 2004-2014. The regression curve estimation shows that PaO₂–mortality relationship is a quadratic function (U-shaped curve).

Figure 2 - PaO₂– SMR

Panel A and B. The relationship between partial pressure of oxygen (PaO₂) and the modified standardized mortality ratio and standardized mortality ratio (SMR). The modified SMR was calculated by excluding the FiO₂ / PaO₂ coefficient from the PIM2 calculation. SMR was calculated using the pediatric index of mortality 2 (PIM2) score. The grey dashed lines represent upper and lower confidence intervals.

Figure 3 - Flowchart systematic review

Flowchart showing the selection of hypoxia and hyperoxia studies.

Figure 4 - Forrest plots

Forrest plots of hypoxia (4A) and hyperoxia (4B) studies. The estimate assessed is the odds ratio of death with hypoxia/hyperoxia. I^2 is the measure of heterogeneity. The width of the horizontal line for each study represents 95% confidence interval (CI). The red vertical dashed line represents the overall odds of death. The blue rhomboid represents the 95%CI of the overall odds ratio.