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Oxygen Toxicity in PARDS

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Introduction

We administer supplemental oxygen as part of our initial care for an acutely ill child. Our peers, and the public, expect us to do so. The practice is supported in guidelines such as Advanced Paediatric Life Support[1]. We know that oxygen is necessary for efficient mitochondrial production of high energy phosphates in that complex process of mitochondrial 'oxidative phosphorylation'[2]. We cannot survive long underwater, in space or in a smoke-filled room because of a lack of oxygen in these environments leads to mitochondrial energy failure and death in minutes.

On the other hand, oxidation is something we know to be bad. Oxidation is a loss of electrons from a substance as they are extracted by oxygen to complete the two singlet pairs in its outer shell. Oxidation destroys things. Metals rusting, food rotting, and probably animals aging are, at least in part, accumulation of oxidative injury over time. From his original discovery of oxygen, Joseph Priestley was aware of this potential for harm "...for, as a candle burns out much faster in dephlogisticated [oxygen] than in common air, so we might, as may be said, live out too fast and the animal powers be too soon exhausted in this pure kind of air."

The mediators of oxidative injury are 'reactive oxygen species' (ROS). These are oxygen containing molecules that are vigorously seeking to collect electrons. Importantly, the partial pressure of oxygen in an individual cell influences the rate of ROS production as a by-product of oxidative phosphorylation in the mitochondria. Humans have a buffer system of antioxidant molecules that can neutralise a modest concentration of ROS. However, these are overwhelmed when ROS concentrations rise[3]. When this happens, the system is said to be in a state of 'oxidative stress' or reduction-oxidation (redox) imbalance. If sufficiently severe this can destroy critical cellular components (DNA, proteins, and lipids). Cell death can follow.

Supplemental oxygen therapy therefore has potential to cause harm as well as benefit. Intensive care doctors are very aware of the risk of hypoxic-ischaemic death. Indeed, most have seen it happen many times in refractory shock or respiratory failure. In contrast, few if any of us, could recall a case who died from oxygen toxicity. Cell death from oxidative injury may look very similar to other inflammatory causes of cell injury. Clinicians are

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human and naturally prioritize visible and proximate risks above the more opaque and distant ones. Not doing so would leave oneself open to criticism from peers, parents and even the courts.

We are starting to understand the complex risks of benefits of supplemental oxygen in paediatric critical illness. A u-shaped relationship exists between admission levels of arterial oxygen tension and risk-adjusted mortality[4,5] (Figure 1). Of course, this observation may be confounded by unmeasured clinician concern for leading to more aggressive oxygen supplementation in sicker patients. Our current practice is biased towards liberal oxygenation – an peripheral oxygen saturation (SpO_2) value of 100% is by far the most commonly seen on paediatric intensive care units[6,7].

Indirect evidence of harm from oxygen across acute illness in adults is summarised in Chu et al's systematic review and meta-analysis of oxygen[8]. Here, data from 16 037 patients in 25 randomised controlled trials which compared conservative to liberal oxygen administration in various scenarios including stroke, emergency surgery, myocardial infarction, sepsis and critical illness, were analysed. More liberal oxygen therapy was associated with a higher mortality than more conservative oxygenation, without improving other patient-important outcomes (relative risk 1·21, 95% CI 1·03–1·43).

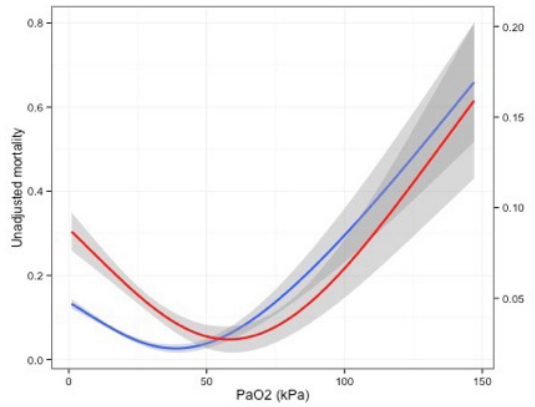

Figure 1 Relationship between arterial oxygen tension and crude mortality (blue line left x-axis) and PIM2 case-mix adjusted mortality (red line right x-axis) and 95% confidence intervals in 7410 critically ill children 2004-2014. Regression curve estimation confirms the PaO2-mortality relationship is a quadratic 'U-shaped' function

Randomised clinical studies evaluating different of oxygen saturation targets are more directly relevant to paediatric critical illness. The BIDS trial included 615 ward admissions with bronchiolitis allocated to an to SpO_2 target of >94% or >90%. These were equivalent in terms of safety and clinical effectiveness[9]. The >90%target was associated with a reduction in time receiving oxygen 27.6 (0 to 68.1) hours vs 5.7 (0 to 32.4) hours hazard ratio 1.37 (1.12 to 1.68), p=0.0021 and time to discharge 50.9 (23.1 to 93.4) vs 40.9 (21.8 to 67.3), p=0.003. Our recent pilot Oxy-PICU trial recruited 120 emergency paediatric intensive admissions receiving mechanical respiratory support early (<6 hours from first contact with intensive care staff). Randomisation was to a more restrictive oxygen therapy SpO_2 target (88-92%) or standard care (SpO_2 >94%)[10] (Figure 2). No safety concerns were identified, and a definitive trial is being planned which aims to recruit 2040 patients from 15 centres. Two trials in critically ill adults also hint towards benefit in the conservative oxygenation group – especially in the sub-populations with more severely abnormal gas exchange[11,12]. Larger scale trials are underway and the first, ICU-ROx, anticipated to report later this year[13].

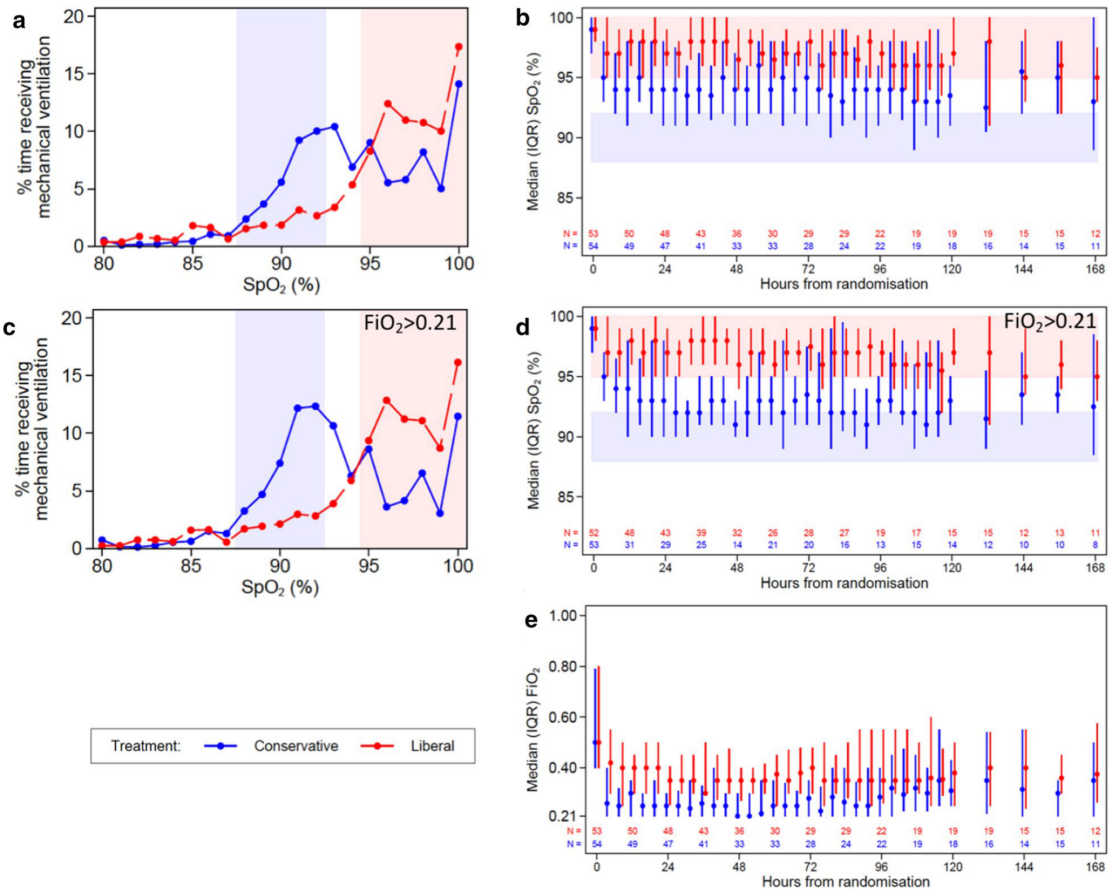

Figure 2 Distribution of SpO_2 and FiO_2 by treatment group. The percentage of time at each SpO_2 over the PICU stay (a, c) and median (IQR) SpO_2 (b, d) and FiO_2 (e) measurements at individual timepoints for the first 7 days following randomisation are shown. a, b, e Show all mechanically ventilated timepoints whereas c, d show only SpO_2 values in children mechanically ventilated with FiO_2 > 0.21. Shaded areas illustrate the treatment group target SpO_2 ranges. Reprinted with permission from reference 10.

Before we rush to lower our oxygen targets while awaiting these data, we should take note of the similar studies in extreme premature infants. 4965 infants less than 28 weeks' gestation were randomised to lower (85%-89%) vs higher (91%-95%) oxygen saturation targets in a total of 5 trials. There was no net benefit or harm on death or major disability at a corrected age of 18 to 24 months[14]. There were increases in mortality in the lower target group alongside decreases in retinitis of prematurity and necrotising enterocolitis.

So, we currently have no high-grade evidence for choice of oxygen targets in acutely ill children with acute lung injury or acute respiratory distress syndrome (ARDS). The PEMVECC guidance recommends more conservative targets of 88-92% in more severe cases[15]. The point at which the risks of this approach outweigh the benefits cannot currently be known. This balance may be determined by which of the two main candidate mechanisms for oxygen-mediated harm predominates. It is possible that a high SpO_2 is not harmful in itself but that the interventions provided to achieve it in a critically ill child may be. The heavy sedation, higher mean airway pressure and FiO_2 could lead to harm independent of the oxygenation status.

Thus, any benefit from tolerating a lower SpO_2 may simply be avoiding an iatrogenic injury. Of course, there may also be a contribution from high levels of oxidative stress from higher tissue oxygen tensions. Or more likely some combination – which will vary case by case influenced perhaps by duration, peak levels of support and underlying risk.

Conclusions

Whilst we await data from ICU-ROx, Oxy-PICU and other trials, should all be aware both of the potential for generous oxygen administration to cause harm but also the lack of any definitive evidence on which to change practice at this stage.

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Funding
This work including the Oxy-PICU trial was funded by Great Ormond Street Hospital Children's Charity. Registered Charity No. 235825 and supported by the National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.