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Editorial

Is there clarity on the horizon for peri-operative oxygen therapy?

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Recently in *Anaesthesia*, Frei et al. reported initial internal pilot data from the hospital operating theatre randomised oxygen (HOT-ROX) trial currently in progress in Australia and New Zealand [1]. Randomised trials to evaluate the benefits of delivering different concentrations of oxygen around the time of major surgery are not novel and much has been published in this domain over the past 20 years. Yet, we are arguably further away from knowing the answer to how much oxygen we should give to patients undergoing surgery than we were at the beginning of this long journey that has been punctuated by confusion, controversy and research fraud.

Does it really matter how much oxygen we give to patients during and after surgery? Surely as long as a reassuring tone continues to emanate from the monitor with each beat of the patient's heart, we are doing a great job? This may be the case but there is a growing body of evidence to suggest that we may need to give peri-operative oxygen therapy a little more consideration. Oxygen is essential for the maintenance of bioenergetic homeostasis, cellular viability and optimal organ function. Hypoxaemia can result in cellular hypoxia, which will have obvious detrimental consequences and clinical outcomes; therefore, ensuring normoxaemia would seem sensible. The far more contentious issue, however, is whether providing liberal oxygen therapy (a fraction of inspired oxygen (F_iO_2) of up to 0.8) results in better or worse postoperative outcomes. Those in favour of high concentration oxygen argue that it results in a neutrophil 'oxidative burst', inactivating bacteria that would otherwise cause surgical site infections (SSIs) [2] and early trial data supported this hypothesis [3]. Those opposed to oxygen being used in this way cite evidence highlighting the increased incidence of atelectasis with high peri-operative F_iO_2 [4,5], which could lead to significant complications [6]. In patients who are critically unwell and whose lungs are mechanically ventilated, high concentrations of oxygen may have more sinister effects. These include the development of an intense pulmonary inflammatory response [7] and increased mortality in patients with septic shock [8].

While no prospective randomised trial data exists to support the philosophy that peri-operative hypoxaemia has a detrimental effect on clinical outcomes, maintaining normoxaemia throughout such a physiologically challenging period seems rational. Yet, this is not a common approach to oxygenation in the operating theatre. Erring on the side of caution and maintaining supranormal arterial oxygenation via the administration of a moderate increase in F_iO_2 (approximately 0.5) appears to be the norm [9,10]. Although the reasons for maintaining such hyperoxaemia are unclear, a commonly cited reason is the creation of an oxygen 'reserve' (or 'buffer') in readiness for an unintended intra-operative catastrophe. In this case, why not turn the dial up even further, to an

F_iO_2 of 0.8, given that this remains the World Health Organization (WHO) recommendation for peri-operative oxygenation in order to reduce SSIs [11,12]?

The WHO recommendation does not appear to be followed by most anaesthetists and the reason(s) for our reluctance to provide an F_iO_2 of 0.8 are even more elusive than those underpinning the choice of an F_iO_2 of 0.5. Surely given the opportunity, every anaesthetist would be willing to contribute to reducing the risk of SSIs. Perhaps our unwillingness to abide by the WHO recommendation is because critical appraisal of the systematic review and meta-analysis that these were based on highlighted a number of fundamental flaws in the use and interpretation of the evidence available at the time [13]. Or maybe it is because evidence included in the meta-analysis has since been retracted due to data fraud [14,15]. But it may also be due to a growing understanding that oxygen is not a benign drug and its use at higher concentrations is not without risk across a wide range of clinical scenarios [16].

A desire to summarise the evidence evaluating the efficacy of high concentration oxygen to reduce SSIs has led to the publication of as many systematic reviews and meta-analyses as there are trials. Each of them presents a unique cohort of data and therefore often draws conflicting conclusions; which is why there is now a need to conduct an overview of all these systematic reviews and meta-analyses [17]. However, Frei et al. may be able to shine a new light on this perplexing situation by starting afresh with the large-scale, multi-centre trial, HOT-ROX [1].

Like many peri-operative oxygen trials before it, HOT-ROX is recruiting adult patients undergoing non-cardiac procedures; most of the first 210 patients initially reported were male (over 64%), of European ethnicity (over 81%) and having an elective procedure (over 99%). However, unlike most previous studies, HOT-ROX is specifically recruiting patients who are sicker (ASA physical status 3 or 4 only) and undergoing longer procedures (minimum duration 120 min) across a wide range of surgical specialties. Of note, only a third of these initial 210 patients had metastatic disease. How this specific group of surgical patients will respond to the interventions remains to be seen, but the HOT-ROX triallists clearly believe this is the patient cohort most likely to benefit from a change in current peri-operative oxygen strategies. By selecting the primary outcome measure to be days alive and at home at 30 days (DAH_{30}), the triallists also expect any benefit to include a reduction in morbidity and not just mortality. Composite outcome measures of this type are becoming increasingly common in peri-operative trials, but a 30 day follow up will be considered relatively

short by some and will almost certainly be too short to capture the full recovery of many patients in this sicker cohort undergoing lengthier operations.

Refreshingly though, HOT-ROX has finally broken a dogmatic tradition followed by almost all previous peri-operative oxygen trials and not only randomised to either an arbitrary 'high' (almost universal F_iO_2 of 0.8 as in HOT-ROX's 'liberal' group) or 'low' (often F_iO_2 of 0.3, or the minimum F_iO_2 needed to achieve SpO_2 93% in HOT-ROX's 'restrictive' group) concentration of oxygen while the patient is in the operating theatre. Instead, HOT-ROX includes a third 'usual care' group (where the F_iO_2 is kept between 0.4 and 0.6 in the operating theatre) and the interventions continue postoperatively into the post-anaesthesia care unit/intensive care unit. Promisingly, the results from the initial planned analysis reported that good group separations were achieved overall, particularly during surgery. However, it is slightly disappointing that the F_iO_2 separation was not quite as pronounced postoperatively, with a particularly wide range of values in the liberal group, and relatively similar median values across both the restrictive and usual care groups. Given that patients often receive supplemental oxygen for proportionately longer lengths of time postoperatively than they do intra-operatively, the median postoperative study time of around 2 h across the three groups suggests HOT-ROX is only focusing on the very early parts of the patients' recovery. It is also interesting that the triallists chose not to protocolise other aspects of anaesthetic care except for the F_iO_2 itself and left these other decisions to the discretion of the treating clinicians. This included ventilation parameters such as positive end-expiratory pressure, which could also be expected to impact on oxygenation status.

At this early stage, the results of the HOT-ROX trial are understandably limited to the feasibility of completing the rest of the study and only pooled results (and no inter-group comparisons) of the primary and secondary outcomes are reported. Nevertheless, the pre-specified feasibility outcomes have all strongly supported the trial continuing unchanged. Reporting no serious adverse events in the first 210 patients should help encourage new sites to join when recruitment spreads beyond the four centres currently enrolling participants; reassure any clinicians with reservations about turning their oxygen dial up or down; and provide the confidence needed by patients regarding trial safety.

What are we likely to learn from HOT-ROX once an analysis of all 2400 patients has been completed? The trial was designed to test two separate hypotheses; whether a restricted approach to oxygenation would increase DAH_{30} and whether a liberal approach to oxygenation would reduce DAH_{30} (both compared with standard care). So, in effect HOT-ROX is actually two overlapping trials,

each consisting of 1600 patients. The sample size calculation was based on an ability to detect a median difference of 1 day (for DAH_{30}) between each intervention group and standard care, although it has been suggested that the minimal clinically important difference for DAH_{30} could be as many as 3 days [18]. Importantly, the HOT-ROX trial has the potential to explore whether any relationship between oxygen therapy and clinical outcomes is linear in nature. The trial is powered to investigate the effect of both more and less oxygen (when compared with the middle-ground of usual oxygen therapy), which is unusual among oxygen therapy trials. A comparable approach was taken in a recently published trial evaluating oxygen saturation targets among patients who were critically ill and required mechanical ventilation [19]. So, the HOT-ROX trial may be able to tell us whether 'less is more' and if 'more is less'. Yet if both interventions lead to an increase (or decrease) in DAH_{30}, this trial may leave us a little puzzled about what to do next.

Even if the HOT-ROX trial produces definite findings, this will not be the end of the journey to optimise peri-operative oxygenation for our patients. Human physiological research has repeatedly shown us that all biological processes exhibit heterogeneity, particularly in terms of our responses to oxygen availability [20]. Once we have established the framework within which future trials should operate, our approach to determining how much oxygen the patient we are just about to anaesthetise needs may have to be guided by more complex approaches that include genetics; epigenetics; advanced biomarkers; and (yet to be developed) tissue oxygen monitoring systems. Perhaps a conundrum for the next generation of investigators to ponder on.

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