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Past, present and future of conservative oxygen therapy in critical care

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Title: The past, present and future of conservative oxygen therapy in critical care

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Conservative oxygen therapy

Conservative oxygen therapy (COT) is the administration lower levels of supplemental oxygen than usual in order to tolerate a lower level of arterial oxygenation (either the partial pressure (PaO_2) or haemoglobin saturation (SaO_2)) than normal. Its purpose is to reduce a patient's overall exposure to additional oxygen in order to minimise the risk of oxygen toxicity.¹ This approach to oxygen therapy has also been called permissive hypoxaemia (PH) and the terms are frequently used interchangeably; here, we refer to all efforts to reduce supplemental oxygen administration or arterial oxygenation as COT. Studies have been conducted across a wide range of medical conditions, to determine whether COT improves patient outcomes and there appears to be a signal of benefit among acutely unwell patients.² The intention in this article, however, is to focus only on critically ill patients admitted to intensive care units (ICUs). These patients often present with acute hypoxaemic respiratory failure and require high concentration oxygen to restore normal arterial oxygenation. There is concern that one of the central pillars of support for these patients, oxygen, may inadvertently be causing them harm, which we mistakenly ascribe to a worsening of their underlying pathology. There remains no consensus on how or when to use COT in critically ill patients and it is imperative we address these questions as soon as possible.

The past

Prior to the COVID-19 pandemic, a number of observational studies sought to understand the relationship between arterial oxygenation and survival using data from retrospective databases. Some findings supported the notion that hyperoxaemia was associated with harm³ while others did not⁴. These early studies tended to rely on an extremely limited quantity of routinely collected data, commonly only using a single oxygenation value per

patient. Their findings were at high risk of confounding by treatment indication and provided no information about causality. More recently, investigators have attempted to mitigate the effects of these methodological limitations by using more sophisticated analytical techniques, with results indicating a clear signal of harm in critically ill patients exposed to hyperoxaemia.⁵ Randomised controlled trials (RCTs) have also been conducted to determine whether there are clinical benefits to implementing COT and new data continues to emerge. The most recent syntheses of these data concluded that there is no clear signal of benefit or harm for COT in critically ill patients.^{6,7} It is clear from the forest plots in these meta-analyses that the RCTs conducted and reported to date have not yielded consistent results. This, in part, is likely due to differences in study design in terms of: the type of patients recruited; interventions evaluated; and the management of oxygenation in the comparator group; making interpretation of the results of the meta-analysis extremely difficult. It is also worthy of note that by creating a comparator group in which hyperoxaemia is encouraged, the effectiveness of the COT intervention (if one exists) is highly likely to be exaggerated if excessive oxygen is harmful. There is also an overlap of COT and comparator targets within some of the studies. Furthermore, studies either exclusively recruited, excluded or were ambivalent to severe hypoxaemic respiratory failure; and include a mixture of mechanically ventilated and spontaneously breathing patients with various pathologies. Whilst some of these factors are difficult to resolve in the setting of an ICU, due to the innate heterogeneity of critically ill patients, the wide variation in intervention and control parameters in these studies means there is not yet a clear conclusion to the question.

The present

The COVID-19 pandemic is far from over and at the time of writing, the new Omicron variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was rapidly spreading around the planet. During the early stages of the pandemic, little data existed to

aid clinicians in making informed decisions about the use of COT.⁸ The pandemic disrupted healthcare systems (and clinical research programmes) around the world and brought with it a sobering reminder that we have yet to establish evidence-based answers about the how or when of COT. Consequently, COT could not be recommended as a beneficial therapeutic intervention for mechanically ventilated patients with COVID-19 pneumonitis. The number of hypoxaemic patients in hospitals was unprecedented and pushed hospitals to their breaking-point in terms of providing adequate and safe respiratory support for patients. Healthcare systems were forced to consider the unthinkable consequences of local oxygen demand exceeding supply. In response to this in the United Kingdom (UK), national guidance from the British Thoracic Society advised that the usual peripheral oxygen saturation (SpO₂) target for an acutely unwell adult patient of 94-98%⁹ should be modified to 92-96%. National guidance in the UK also suggested that further reduction to an SpO₂ of 90-94% should be considered, if deemed clinically appropriate and continuous patient monitoring available. Similarly, NHS England (NHSE) guidance on the management of critical care for adults with COVID-19, endorsed by the Intensive Care Society and the Faculty of Intensive Care Medicine, recommended an SpO₂ target of 90-93% as acceptable in patients with visible continuous pulse oximetry in appropriately monitored care environments with trained staff to monitor for clinical deterioration.¹⁰ Findings from the improving oxygen therapy in acute-illness (IOTA) systematic review and meta-analysis were used to support these national recommendations; even though the meta-analysis being dominated by patients admitted with myocardial infarction and stroke rather than respiratory failure.²

Despite the lack of evidence to support COT for critically ill patients with COVID-19, it was commonplace in the UK for patients on an ICU to be managed according to the national guidance or with even lower SpO₂ targets (e.g. 88 to 92%). A survey conducted in the UK during May 2020 indicated that the majority of respondents were comfortable using COT.¹¹ We will never know whether this was the right thing for those patients as it was never

formally evaluated within an RCT. A small post-hoc subgroup analysis of the HOT-ICU trial assessed the impact of COT in just 110 patients with COVID-19 and found a non-significantly lower 90 day mortality in the COT cohort (40.7% versus 41.8%, adjusted risk ratio 0.87, 95% confidence interval 0.58 to 1.32).¹² Based on this finding the authors are currently conducting the handling oxygenation targets in COVID-19 (HOT-COVID) trial (<https://clinicaltrials.gov/ct2/show/NCT04425031>), an adaptation of their HOT-ICU trial¹³ that will continue to evaluate a PaO₂ target of 60 versus 90 mmHg in 780 acutely ill adult patients with COVID-19 and hypoxaemic respiratory failure. As a result of the ongoing COVID-19 pandemic there appears to be a general feeling amongst clinicians that they are now more comfortable with the use of COT in severely unwell mechanically ventilated patients. However, there is a risk that this slowly metamorphoses into the belief that this intervention is actually therapeutically beneficial compared to normal oxygenation. This potential collapse of clinical equipoise, without evidence to support the hypothesis, could impact the ongoing trials seeking to evaluate COT. For a RCT to be feasible, one important element, clinical equipoise, is *essential*; there must be sufficient clinical uncertainty as to whether the intervention to be evaluated is superior to either standard therapy or placebo (the comparator).¹⁴ If there is consensus that the intervention in question is superior to the comparator, the ethics of the trial become undermined and attempting to persist with gaining an answer to the research question may become impossible. Clinicians will not recruit participants into a trial to which they believe the answer is already known. What we must also remember is that COVID-19 is a specific disease entity, the likes of which we have never encountered before, therefore therapies we believe to be effective during the pandemic may not be applicable to critically ill non-COVID-19 ICU populations. To this end, we should be extremely cautious about “learning lessons” from practices that have taken place under the extraordinary circumstances that accompanied this pandemic, and applying them to our non-COVID-19 critical care practice. During the pandemic, it was imperative that we reacted rapidly to newly generated and sometimes incomplete evidence, however, we

should not let this degrade a robust approach to the generation of evidence-based care when normality resumes. It would be a matter of great regret if the trend for unnecessary hyperoxaemia in ICUs in the late 20th century and early 21st century, which was the consequence of non-evidence-based clinical habits and beliefs at that time, was replaced by a similar non-evidence-based set of clinical habits and beliefs favouring hypoxaemia in the third decade of the 21st century.

The future

As we emerge from the COVID-19 pandemic it is crucial that as a specialty we continue our exploration of COT in critically ill patients, building on the evidence base that preceeded it.

Looking forward, two large multicentre RCTs are evaluating the benefit of COT in mechanically ventilated critically ill patients; Mega-ROX

(<http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379432&isReview=true>) is global and UK-ROX (<https://www.isrctn.com/ISRCTN13384956>) UK-based. Aiming to recruit large numbers (40,000 participants for Mega-ROX and 16,500 for UK-ROX), these two trials have been prospectively designed to allow for an individual patient data meta-analysis on completion. Using novel trial designs to ensure rapid accomplishment of such large trials, the trial investigators are calling on intensive care communities around the world to help answer their questions as rapidly as possible. We are unlikely to have a clear conclusion to the COT story until both of these RCTs have reported their results. Until then we must consider this simple therapeutic intervention to be experimental and maintain an open mind about whether it is beneficial, harmful or neither.

Conclusions

Prior to the COVID-19 pandemic we did not know whether we should be using COT in mechanically ventilated patients and the pandemic has not altered this. There was insufficient evidence to recommend COT then and there is insufficient evidence to recommend COT now. The recommendation to aim for lower SpO₂ values than usual during

the COVID-19 pandemic was a logistical necessity and when that necessity has subsided, we should be reminded to revert to our previous practices until further evidence emerges.

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