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Editorial

Is less really more for oxygen therapy in patients with acute respiratory failure?

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Oxygen is a universal therapy for intensive care unit (ICU) patients with acute respiratory failure. Until recently, relatively few data from randomised controlled trials were available to guide clinicians as to how much oxygen to give to patients in the ICU [1–3], and even less were available for patients with acute respiratory failure specifically [4]. While liberal provision of oxygen provides a greater margin of safety against hypoxaemia, in patients with acute respiratory failure, it also potentially exposes diseased lungs to greater oxidative stress, and may also result in higher chance of inadvertent systemic arterial hyperoxaemia and tissue hyperoxia. Accordingly, given how widely oxygen is used, the question of how much oxygen to give is an important one.

In 2020, investigators from the European Research Network in Artificial Ventilation (Réseau Européen de Ventilation Artificielle – REVA), reported the findings of the Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome (ARDS) trial ($LOCO_2$) [4]. The trial was stopped prematurely by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. At day 28 (the primary outcome), a total of 34 out of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). Of particular concern, five mesenteric ischemic events occurred in the conservative-oxygen group. These data raised concerns about the potential for harm with restrictive oxygen therapy regimens in patients with ARDS.

Over the last 12 months, the Coronavirus Disease 2019 (COVID-19) pandemic has resulted in unprecedented worldwide demand for supplemental oxygen therapy for ARDS patients. In many parts of the world, the demand for oxygen during the COVID-19 pandemic has exceeded, or threatened to exceed, the available oxygen supply. Facing oxygen supply constraint provides a strong impetus to use oxygen conservatively, and has created a heightened sense of urgency with respect to whether or not the signal of harm suggested by the $LOCO_2$ trial [4] was a chance occurrence. The Handling Oxygenation Targets in the ICU (HOT-ICU) trial [5] provides important new data on this issue.

The 2928-participant HOT-ICU trial [5] was a multicentre, international randomised clinical trial evaluating oxygen regimens in adults with acute hypoxic respiratory failure. The primary outcome, 90-day mortality, was not significantly different for patients assigned to lower *vs.* higher oxygenation targets. The percentage of days alive without life support, days alive after hospital discharge, and adverse events, including intestinal ischemia, were also similar by treatment group.

For clinicians from France, particularly in sites that contributed to the $LOCO_2$ trial [4], the apparent discordance between these two trials [4,5] is of particular interest, because, all other things being equal, the French study would be expected to be more generalisable to French ICUs. The participants in the $LOCO_2$ trial [4] were adults with ARDS, while those in the HOT-ICU trial [5] were adults in the ICU with acute hypoxic respiratory failure who required >10 L of oxygen via an open system or an inspired oxygen concentration of $\geq$ 0.5. Both trials used a 12-h enrolment window and although these patient populations are different, it seems very likely that there was considerable overlap between them. The intervention in the $LOCO_2$ trial [4] was conservative oxygen therapy, which was defined as a target PaO_2 of 55–70 mmHg and oxygen saturation as measured by pulse oxymetry (SpO_2) of 88–92%, whereas in the HOT-ICU trial [5], a PaO_2 target of 60 mmHg was used. In the $LOCO_2$ trial [4], data from six hourly arterial blood gases over the first seven days were reported, whereas in the HOT-ICU trial, the median of the average of the highest and lowest daily arterial blood gas for up to 90 days was reported. Despite differences in the reporting of oxygen metrics, the reported PaO_2 was $\approx$ 70 mmHg for the conservative oxygen therapy groups in both trials. A total of 58 patients in the conservative arm of the $LOCO_2$ trial [4] had at least one arterial blood gas measure with a PaO_2 of less than 55 mmHg. Although similar data were not reported in the HOT-ICU trial [5], it is possible that more patients in the $LOCO_2$ trial [4] were exposed to extreme hypoxaemia. The comparator in the $LOCO_2$ trial [4] was a target PaO_2 of 90–105 mmHg and an oxygen saturation as measured by pulse oxymetry (SpO_2) of $\geq$ 96%, and in the HOT-ICU trial [5] was a target PaO_2 of 90 mmHg. The reported PaO_2 values in the liberal arm of the $LOCO_2$ trial [4] were around 10 mmHg higher than were reported in the higher oxygenation group in the HOT-ICU trial

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[5]. However, because arterial oxygenation data were reported in different ways in the two trials, it is uncertain whether this difference in reported PaO_2 values represents a true difference in oxygen exposure in the liberal arms of the respective trials. The primary outcome of the $LOCO_2$ trial [4] was 28-day mortality and the primary outcome of the HOT-ICU trial [5] was 90-day mortality. While neither trial reported a statistically significant difference in the primary outcome, in both trials the lowest mortality rate occurred in groups in which oxygen was administered most liberally. While there are some differences between these trials, the bottom line is that they investigated broadly similar treatment regimens in broadly similar patient populations. As the HOT-ICU trial [5] was $\approx$ 15 times larger than the $LOCO_2$ trial [4], the apparent increase in mesenteric ischaemia with conservative oxygen therapy in the $LOCO_2$ trial [4] now appears likely to represent a chance finding rather than a true effect. Despite some differences between the trials, neither one provides a strong rationale for implementing conservative oxygen therapy regimens in patients with ARDS. Nevertheless, in situations where oxygen supply is constrained, conservative oxygen therapy can reasonably implemented on the basis of the HOT-ICU trial [5] data.

HOT-ICU [5] represents an important advance in knowledge, but it is important to note that, even in the HOT-ICU trial [5], the 95% confidence interval (CI) around the 90-day mortality treatment effect encompasses the possibility of a 2.9 percentage point absolute reduction and a 4.2 percentage point absolute increase in mortality with conservative oxygen therapy. Further research is now needed to definitively establish whether conservative oxygen therapy is beneficial or harmful in ICU patients with acute respiratory failure [6]. Given how frequently oxygen is used in clinical practice on a global scale, obtaining precise estimates of the range of potential mortality treatment effects attributable to conservative or liberal oxygen therapy is a high priority.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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