Oxygen therapy in the critically ill: *Less is the new more?*

The evolution of medicine is not limited to the development of new therapies albeit extends to the most pragmatic application of those existing. As the concept of precision medicine dawns, the fraternity is equally focusing at the harms of overzealous treatment. The paradigm shift of "less is the new more" is already making a mark in the modern medicine along the lines of a great Paracelsus saying: "All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison."

Appropriate to the aforementioned context, oxygen, the most ubiquitously used therapeutic agent, essentially classifies as a drug with characteristic physiological–biochemical properties and a range of effective dosages. Oxygen therapy (administered with the fundamental aim of minimizing cellular hypoxia) can potentially demonstrate peculiar deleterious effects at higher concentrations. Although the physicians administer oxygen therapy in diverse clinical scenarios, such as resuscitation, perioperative period, and intensive care unit (ICU), the considerations for the detrimental effects of prolonged hyperoxia in the critically ill cohort become manifold.

There is a substantial recent literature accumulating in this research area. The oxygen-ICU randomized clinical trial (RCT) involving 480 critically ill participants (with an expected ICU stay ≥72 h) outlined a significantly lower mortality rate of 11.6% with a conservative oxygenation approach [partial pressure of arterial oxygen (PaO_2) of 70–100 mmHg or 94–98% target arterial oxygen saturation (SpO_2)] compared to a 20.2% mortality rate in the more liberal regime allowing a PaO_2 upto 150 mmHg or 97–100% target SpO_2.[1] In addition, a broadly inclusive systematic review and meta-analysis, "Improving Oxygen Therapy in Acute illness" comprising of 25 RCTs amounting to a total of 16,037 patients with underlying critical illness (sepsis, myocardial infarction, stroke, post-cardiac arrest, emergency surgery, etc.) demonstrated a high-quality evidence for the mortality reduction effect of conservative oxygenation robust to a subsequent trial sequential analysis.[2]

The clinical applicability of the meta-analysis results has been interrogated by the practitioners citing a wide range of heterogeneity of the included RCTs with a few RCTs employing a much more liberal oxygenation approach than the usual care. Withstanding this fact, the "Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy" (ICU-ROX) revealed an insignificant difference in 90-day mortality in a comparative evaluation of the conservative oxygenation strategy (91–97% SpO_2) with a usual-care strategy (91–100% SpO_2). Despite comparable mortality between the two strategies, considerable treatment-effect heterogeneity was appreciated wherein the hypoxic–ischemic encephalopathy subset demonstrated favorable outcomes in the background of conservative oxygenation.[3]This positive modulatory impact has been previously depicted in a multicenter cohort study outlining a heightened mortality with post-resuscitation hyperoxia which is often attributed to the accentuation of secondary injury owing to an enhanced oxidative stress.[4] Moreover, the usual care in this trial did not classify as a hyperoxemic or a liberal oxygen strategy which is in sharp contrast to the previous investigations such as the oxygen-ICU trial.

Prompted by the potential bactericidal properties of oxygen therapy, 442 septic subjects were exposed to a 1.00 fraction of inspired oxygen (FiO_2) for the 1st 24 h in the "Hyperoxia and Hypertonic Saline in Patients with Septic Shock"(HYPERS2S) trial.[5] It is noteworthy that the trial had to be prematurely terminated in view of the unacceptably high mortality rate in the hyperoxia intervention group. However, a *post-hoc* analysis of 251 septic patients from the ICU-ROX trial suggested a 7% higher mortality in the conservative oxygenation group supporting the notion of a beneficial impact attributable to higher oxygen-thresholds in sepsis.[6] Interestingly, their analysis was not powered enough to detect the suggested effects precluding the clinical extrapolation of the aforementioned findings. In addition, an updated meta-analysis including 17 RCTs failed to demonstrate a strong evidence of reduction in the surgical site infections with a higher perioperative FiO_2 (0.80) when compared to a lower FiO_2(0.30-0.35).[7]

To conclude, the presumption of hyperoxia as a panacea is being increasingly challenged. While the most recent Cochrane review in this subject suggests that the elevated fractions of oxygen supplementation may incur an accentuated ICU mortality risk,[8] many debate the generalization potential of these results given the heterogeneous settings of investigation and an inherent research reliance on subgroup analysis, often rendering it difficult to distinguish "signals" from "noise" in this peculiarly predisposed cohort.[9] Nevertheless, the acknowledgement to the precision concept in oxygen therapy[10,11] and an improved characterization of the therapy targets is definitely the need of the hour for optimizing the outcomes in the critically ill.

Rohan Magoon, Neeti Makhija[1], Jes Jose[2]

Department of Cardiac Anaesthesia, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, [1]Department of Cardiac Anaesthesia, Cardiothoracic Centre, CNC, All India Institute of Medical Sciences, New Delhi, Ansari Nagar, [2]Department of Anaesthesia, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi, India

Address for correspondence: Dr. Neeti Makhija, Department of Cardiac Anaesthesia, Room No. 9, 7th Floor, Cardiothoracic Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: neetimakhija@hotmail.com

References

1. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, *et al*. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: The Oxygen-ICU randomized clinical trial. JAMA2016;316:1583-9.
2. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, *et al*. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis. Lancet 2018;391:1693-705.
3. ICU-ROX investigators and the Australian and New Zealand intensive care society clinical trials group; Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, *et al*. ICU-ROX investigators the Australian and New Zealand intensive care society clinical trials group. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med 2020;382:989-98.
4. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, *et al*. Emergency medicine shock research network (EM Shock Net) investigators.Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.
5. Asfar P, Schortgen F, Boisramé-Helms J, Charpentier J, Guérot E, Megarbane B, *et al*. HYPER2S investigators; REVA research network. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S). Lancet Respir Med 2017;5:180-90.
6. Young P, Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, *et al*. ICU-ROX investigators the Australian New Zealand intensive care society clinical trials group.Conservative oxygen therapy for mechanically ventilated adults with sepsis. Intensive Care Med 2020;46:17-26.
7. de Jonge S, Egger M, Latif A, Loke YK, Berenholtz S, Boermeester M, *et al*. Effectiveness of 80% vs 30-35% fraction of inspired oxygen in patients undergoing surgery: An updated systematic review and meta-analysis. Br J Anaesth 2019;122:325-34.
8. Barbateskovic M, Schjørring OL, Russo Krauss S, Jakobsen JC, Meyhoff CS, Dahl RM, *et al*. Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. Cochrane Database Syst Rev 2019;2019:CD012631.
9. Magoon R, Jose J. Safeguarding anaesthesia research from spin. Br J Anaesth 2020;125:e460-2.
10. Magoon R. Precision cardiac anesthesia: Welcome aboard! J Cardiothorac Vasc Anesth 2020;34:2551-2.
11. Magoon R. Implications of practice variability: Comment. Anesthesiology 2020;133:943-4.

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_142_20

How to cite this article: Magoon R, Makhija N, Jose J. Oxygen therapy in the critically ill: *Less is the new more?* J Anaesthesiol Clin Pharmacol 2020;36:433-4.

Submitted: 29-Mar-2020 **Revised:** 20-Jul-2020
Accepted: 27-Dec-2020 **Published:** 18-Jan-2021