

## Perioperative oxygen therapy: meaningful outcomes and unintended consequences?

Editor,

The 2016 WHO “Guidelines on perioperative oxygen therapy”<sup>1</sup> have generated considerable controversy<sup>2,3</sup>. In this context, we congratulate the authors of two carefully conducted and tightly focused systematic reviews and meta-analyses of ?? high versus low concentration perioperative oxygen therapy published in the *BJA* of March 2019<sup>4,5</sup>. Rigorous secondary examination of published trial data in this area is an important activity and should be applauded. However, we question the conclusion that “... there is little evidence on safety-related issues to discourage its use in this population.”<sup>5</sup>.

First, the “matrix of outcomes” (Table 4<sup>4</sup>) summarizing the safety data from the 15 primary trials reviewed by Mattishent *et al* reports NR (Not Reported) for 89 out of 120 possible outcome cells. In our view, this absence of evidence for almost three quarters of the possible safety outcomes is not consistent with the reassuring comments about evidence of absence of harm made in this manuscript. Moreover, the risk of harm from high levels of perioperative oxygen therapy has been highlighted by a number of commentators<sup>2,3,6</sup> and emphasized by the findings of the recent IOTA systematic review and meta-analysis<sup>7</sup>. The IOTA authors concluded “In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes.”<sup>7</sup>, albeit from an analysis from which studies of patients undergoing elective surgery were excluded.

Second, both systematic reviews comprise a majority of small (<500 patient), single-centre studies, a situation well recognized to be associated with a substantial risk of bias when compared with subsequent definitive large studies<sup>8</sup>. Furthermore, the integrity of data from several of these studies in this area authored by Schietroma *et al*. has been called into question by the recent article by Myles, Carlisle and Scarr<sup>9</sup>. Although not included within the *BJA* systematic reviews, such uncertainty about data integrity in relevant studies further muddies the waters with respect to extracting a clear message from the accumulated literature.

Third, the summarised literature is notable for focusing on two extremes of oxygen therapy: 30-35% and 80% fraction of inspired oxygen. Neither of these approaches is representative of what we currently know to be standard care (observational data from the UK suggests that 41-55% FiO<sub>2</sub> is administered in most cases<sup>10</sup>), and neither of which has any clear biological rationale. Studies taking a titration or dose-response approach to this problem are lacking.

Finally, the focus on a restricted set of outcomes comprising “safety” and reduction of surgical site infection over other, perhaps more clinically relevant and patient-centered, outcomes risks the unintended consequence of inadvertent harm. The POISE trial of perioperative beta-blockade was an excellent example of a well-intentioned intervention that caused substantial harm when implemented <sup>11</sup>.

International initiatives to address the complex and intricate question of oxygen dosage around the time of surgery are important, but we urge caution about over-interpreting the results of currently published studies. Oxygen is a ubiquitous therapy in modern anaesthesia: modest harms or benefits resulting from difference in perioperative dosing may have substantial impact on healthcare outcomes. Adequately powered definitive trials including comparator oxygen dosages representative of usual care and targeted at patient-focused outcomes are long overdue in this area.

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