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The WHO recommendation for 80% perioperative oxygen is poorly justified

Members of the WHO Guidelines Development Group recently attempted to provide worldwide "evidence-based recommendations" for the prevention of surgical site infections (SSI) by stating:

Adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h [1].

This explicit and strong recommendation has caused considerable concern in the anaesthesia community because it directly contradicts the results of many trials (and a meta-analysis of those trials) which showed no benefit of supplemental oxygen.

The use of an increased inspired oxygen fraction (F_iO_2) has a long history in anaesthesia, intensive care, and emergency medicine. Planned induction and extubation of anaesthesia are conducted with 100% oxygen to enhance safety in the case of airway difficulty. Extra oxygen is also given during general anaesthesia as 21% is rarely sufficient, with concentrations ranging from 30% to nearly 100% depending on case factors and anaesthesiologist preference.

There is considerable reason to expect that supplemental oxygen might reduce the risk of surgical site infection [21]. All surgical wounds become contaminated, and the primary defence against bacterial contamination is oxidative killing by neutrophils, a process that requires molecular oxygen and depends on the partial pressure of oxygen in tissue over the entire physiological range. Consistent with this theory, Hopf et al. [11] showed that surgical wound infection risk was inversely related to tissue oxygenation. Based on these observational data, the Outcomes Research Consortium randomized 500 patients having colorectal resection to either 80% or 30% inspired oxygen [9]. The incidence of SSI was halved from 11.2% to 5.2% ($p = 0.001$). The next study was a small methodologically weak trial in a broader surgical population which reported that infection risk was more than doubled in patients given supplemental oxygen (25% vs. 11.3%, $p < 0.02$ [20]). These studies prompted many others. So far, there have been 6 published trials with 3265 patients reporting positive results with increased F_iO_2 [3, 4, 9, 14, 17, 22]. On the other hand 7 trials including

Table 1 Characteristics of randomized controlled studies using either 80% or 30% inspired oxygen during surgery

Literature	Surgery	Duration (h)	ASA % > 2	SSI overall %	Follow-up (weeks)	NNISS % > 1	Remark
[9]	Colorectal	3.1	16.5	8.2	2	7.0	Stopped
[20]	Abdominal	3.7	22.5	17.6	2	8.3	Stopped
[3]	Colorectal	2.7	26.5	19.6	2	22.0	–
[13]	Colorectal	2.3	0	13.2	2	–	–
[14]	Diverse	3.3	24.5	16.7	4	35.2	–
[8]	C-section	<1	–	18.9	–	–	Stopped
[15]	Laparotomy	2.2	19.0	19.6	4	15.9	–
[4]	Appendectomy	0.5	0	9.5	2	–	–
[24]	C-section	<1	–	10.4	4	–	–
[28]	Diverse	1.4	50	6.9	4	2.3	–
[26]	Injuries	3.8	17.1	14.0	12	–	Stopped
[6]	C-section	<1	5.7	8.3	6	–	–
[30]	C-section	<1	–	13.8	6	–	–
[22]	Gastrectomy	3.0	45	9.4	–	–	–
[23]	Colorectal	3.2	56	21	–	17.3	–
[12]	Colorectal	3.5	9.4	15.7	4	–	–
[2]	Colorectal	2.7	80	35	4	–	–

SSI surgical site infection, *NNISS* nosocomial infections surveillance system risk index, *ASA* American Society of Anesthesiologists Physical Status classification, *C-section* caesarean section.

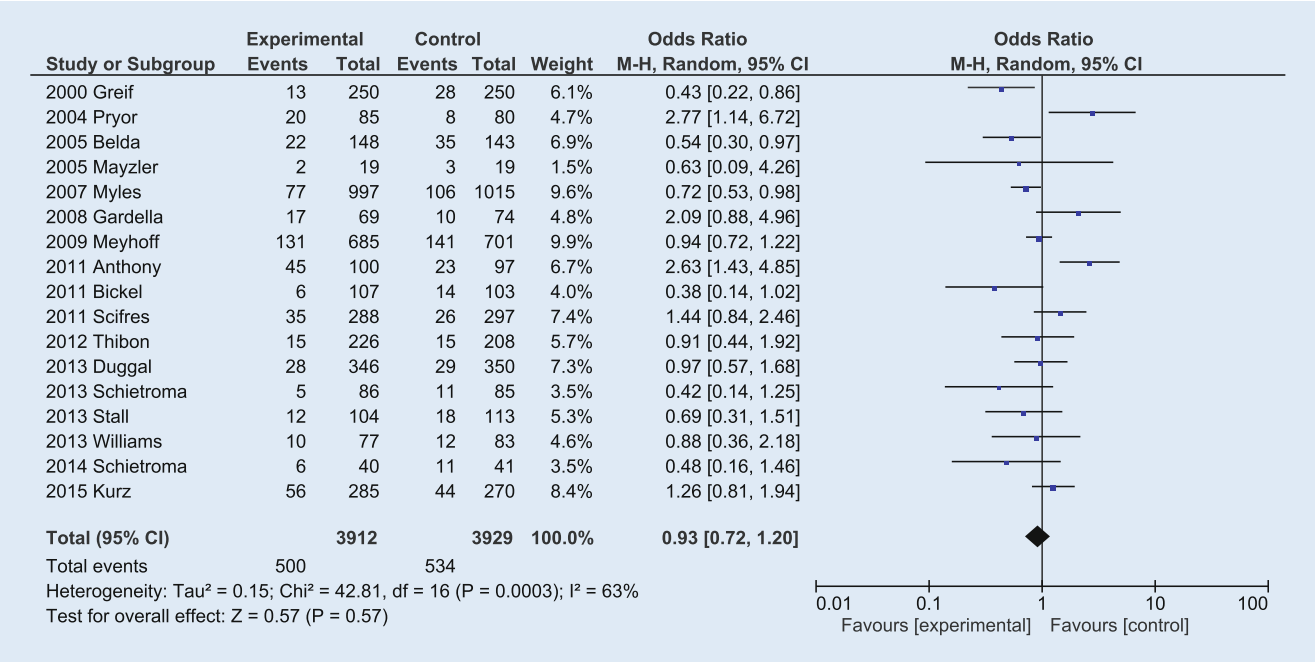

Fig. 1 ▲ Forrest plot and data were calculated using Review Manage Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Data were extracted from the literature represented by year of publication and first author. *MH* Mantel-Haenszel statistical method. A random effects model was used. *CI* confidence interval.

2992 patients reported no benefit of 80% inspired oxygen (**Table 1**) [2, 12, 13, 15, 20, 26, 28].

The WHO panel members based their recommendations on a meta-analysis of 11 randomized trials of supplemental oxygen during and after general anaesthesia. Using a random effects model, they estimated the odds ratio (OR) for SSI as 0.72 (95% confidence interval CI; 0.55–0.94) in favour of 80% inspired oxygen; however, it is quite unclear why the WHO panel excluded studies by Kurz et al. [12] and Anthony et al. [2]. The question is critical because including the results of Kurz et al. [12] and Anthony et al. [2] in the meta-analysis (using the same methodology) yields an OR of 0.84 (CI: 0.62–1.12, p = 0.242), a value that no longer supports this panel's recommendation.

We and the WHO panellists recognize that "ventilation control (and therefore the actual administration of F_iO_2) with a face mask or nasal cannulae in neuraxial anaesthesia (differs) from mechanical ventilation" [1]. But to the extent that increased F_iO_2 protects against wound infection, it should also do so during regional anaesthesia (for example in caesarean deliveries). There are currently 4 randomized controlled reports of 1769 parturients randomized to receive either 80% or 30% inspired oxygen during regional anaesthesia and for 1–2 h thereafter. None of the trials from Seattle [8], St. Louis [24], San Jose [6] and Dayton [9] found that supplemental oxygen reduced infection risk. There is thus not a single trial providing any evidence supporting the recommendation to increase F_iO_2 during regional anaesthesia. Including regional anaesthesia studies in the meta-analysis of all available trials in women yields an OR of 0.93 (95% CI: 0.72–1.2, see **Fig. 1**).

We also note that high inspired oxygen fractions may not be entirely harmless, at least in non-operative contexts. Hyperoxaemia-induced vasoconstriction may be dangerous in patients with critical coronary stenosis [29] and ST-elevation myocardial infarction [27]. The international liaison committee on resuscitation no longer supports the use of supplemental oxygen as long as peripheral saturation (SpO_2) is >94% [18]. Several meta-analyses [5, 19] concluded that hyperoxaemia may be associated with increased mortality in patients with stroke, traumatic brain injury, and those resuscitated after cardiac arrest. Supplemental oxygen may be associated with increased mortality after emergency admissions [25]. Finally, there is mechanistic evidence that high inspired oxygen fractions may be harmful, for example in patients with chronic obstructive pulmonary disease, impaired hypoxic ventilatory drive, or lung failure [10]. Whether supplemental perioperative oxygen is dangerous is much less obvious but Fonnes et al. [7] reanalysed patients randomized in the PROXI trial and found that acute coronary syndrome was nearly twice as common in patients given 80% inspired oxygen. Mortality, despite an initial report [16], appears to be unaffected by supplemental oxygen [19].

The WHO Guidelines Development Group, which curiously included no anaesthesiologists, did not consider all relevant data in their analysis. When all data are included, the results are clear: supplemental oxygen does not reduce wound infection risk. The WHO recommendations, based on selective data, contradict the totality of available evidence and thus fail to provide useful guidance. We recommend that anaesthe-

siologists base their selection of inspired oxygen concentration on considerations other than wound infection risk.

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