


The elusive promise of perioperative hyperoxia

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Arguably, no sphere of contemporary anaesthesia outcomes research has generated more controversy than the question of whether perioperative administration of supplemental oxygen can reduce surgical site infection (SSI). The public health importance of addressing the issue is clear; epidemiological surveys from both England1 and the USA2 show that SSI increases length of stay by ~10 days in colorectal surgery and is associated with substantial excess mortality and cost of care.3 The first randomized controlled trial, published by Greif and colleagues4 in the New England Journal of Medicine in 2000, presented the exciting possibility that a simple perioperative intervention under the control of anaesthetists—delivering 80% oxygen during surgery and for 2 h afterwards—could reduce the incidence of SSI by as much as half. But subsequent attempts to replicate the benefit, including three high-profile randomized controlled trials published in JAMA,5–7 have yielded markedly inconsistent results. Indeed, even meta-analyses of the pooled data are unable to achieve consensus8–11 and have elicited controversy. Studies of other surgeries, including Caesarean section,11 12 have been mostly negative, while secondary analyses have reported...
increased mortality and decreased cancer-free survival in cancer patients receiving supplemental oxygen.\textsuperscript{13, 14}

Much debate has focused on methodological and cohort differences between the trials that might have influenced infection risk or the delivery of oxygen to the site of action. The explanation for the discordant results may indeed be hidden in these differences, but it should not be forgotten that the great pragmatic appeal of perioperative hyperoxia has always been its simplicity and broad applicability. If the benefit is highly nuanced, then the original promise of the intervention is greatly attenuated.

In this issue of the \textit{British Journal of Anaesthesia}, Kurz and colleagues\textsuperscript{15} present a factorial randomized controlled trial of 555 patients undergoing colorectal surgery and report that supplemental oxygen had no effect on SSI. Like its predecessors, this study comes with a unique cluster of design characteristics. It was instituted as a modification of the Hypercapnia and SSI Trial,\textsuperscript{16} approximately halfway through recruitment, and so contains a nested randomization to hypercapnia vs normocapnia. It contains a further nested randomization to dexamethasone 4 mg vs placebo, an intervention the authors concurrently report to have no effect on SSI. Only elective colorectal resections were included; a narrower cohort than evaluated in some other studies, and one which may particularly profit from a high-oxygen-concentration regimen.\textsuperscript{17} The assigned fraction of oxygen was administered for only 1 h in recovery, rather than 2 h. Postdischarge assessments were conducted by telephone interview. Arterial blood gases were measured only through clinical discretion, rather than protocol. Crystalloid infusion was intermediate relative to other studies. And, like all studies, with the exception of the initial trial by Greif and colleagues,\textsuperscript{5} tissue oxygen tension at the site of the wound—critical to the effectiveness of oxidative killing by neutrophils\textsuperscript{17, 18}—was not assessed.

The extent to which these and other aspects of the study might condition interpretation of the results are worthy points for discussion. But this should not distract from the most important, overarching conclusion; that the pragmatic, routine institution of perioperative hyperoxia, however rational, does not produce the desired reduction in SSI.

Kurz and colleagues\textsuperscript{15} reach the same conclusion. In their summary, they write, ‘The preponderance of clinical evidence suggests that administration of 80% supplemental inspired oxygen does not reduce infection risk.’ The significance of that statement is greatly magnified because of who authored it. The present study was conducted by the same outcomes research group responsible for the two major trials that have previously reported a beneficial effect of perioperative hyperoxia: the original trial by Greif and colleagues,\textsuperscript{5, 6} and the trial by Belda and colleagues\textsuperscript{6} published in JAMA in 2005. Given that advocacy for perioperative supplemental oxygen has been heavily driven by support of those two studies, an acknowledgement by this respected group of investigators that the intervention is ineffective represents an important shift in thinking on the subject. At some level, it closes a chapter opened by Greif and colleagues\textsuperscript{5} 15 yr ago. That is not at all to say that this study should signal the end of interest and efforts to identify clinical interventions that can augment oxidative killing in surgical wounds. But the promise of a trivially easy, far-reaching outcome benefit appears elusive.

If oxidative killing by neutrophils is a fundamental mechanism of SSI prevention, and this is dependent on oxygen tension in the wound, then why has perioperative hyperoxia been unsuccessful? A definitive answer to this question is also elusive, but several observations warrant consideration.

Oxygen tension in the wound does not depend solely on the oxygen content of the blood, but also on the specific tissue metabolism and the degree of tissue perfusion. Peripheral vasoconstriction is probably the most frequent and clinically relevant impediment to wound oxygenation.\textsuperscript{18} Hyperoxia has long been recognized to cause such vasoconstriction.\textsuperscript{19, 20} and more recently, has been identified to reduce microvascular perfusion.\textsuperscript{21} High oxygen concentrations decrease cardiac output,\textsuperscript{20} and combined with effects on vascular resistance,\textsuperscript{22} decrease perfusion in several vascular beds; notably, the coronary, cerebral, renal, and peripheral vasculature.\textsuperscript{23–25} Therefore, it is questionable whether an increase in the fraction of inspired oxygen indeed reliably increases oxygen tensions, promoting oxidative killing in the wound. In addition to the direct effects of hyperoxia on small vessels and microvasculature, locally interrupted blood flow resulting from surgical trauma to blood vessels, and local oedema impairing proper gas diffusion, may prevent improved tissue oxygenation despite an elevated oxygen fraction. If regional perfusion decreases as a response to increased blood oxygenation, a seemingly paradoxical situation may occur, in which the administration of oxygen reduces regional oxygen delivery, placing tissues at increased risk of hypoxic stress.\textsuperscript{25}

The mechanisms underlying the oxygen-induced increase in vascular resistance are multiple and complex. High oxygen concentrations increase the production of reactive oxygen species in the vessel wall, which rapidly react with nitric oxide to reduce vasodilator responses.\textsuperscript{26} Other factors, such as hyperoxia-induced hypocapnia,\textsuperscript{27} play an additional but probably less important role. Although it has been shown that a number of reactive oxygen species are components of bactericidal host defenses, they are also involved in several processes that produce tissue injury and inhibit antibacterial mechanisms, such as the antibacterial function of macrophages.\textsuperscript{28} Reactive oxygen species cause cellular dysfunction through damage to DNA, proteins, and increased lipid peroxidation and can induce tissue cell death through apoptosis or necrosis.\textsuperscript{29} Their detrimental effects are in part reflected by the finding that chronic wounds are often characterized by the presence of excessive reactive oxygen species or the absence of antioxidant reactive oxygen species scavenger molecules, such as vitamins E and C and glutathione.\textsuperscript{30}

Physiological s.c. oxygen tension in wounds of normovolemic volunteers breathing room air is ∼65 mm Hg.\textsuperscript{30} Oxygen consumption in wounds is relatively low, and most of the oxygen consumed at the site is used for oxidant production, with other significant contributions dedicated to collagen synthesis, angiogenesis, and epithelization.\textsuperscript{31} The rate constants for oxygen for these components of repair lie within the physiological range of 25–100 mm Hg.\textsuperscript{32} Thus, it appears plausible that the administration of high oxygen concentrations is beneficial only for tissues at or near a critical hypoxic threshold, but that when oxygen supply is sufficient, the effect of oversupply is weighted to the production of reactive oxygen species that may cause tissue destruction. The study by Greif and colleagues,\textsuperscript{5} the only one of the randomized controlled trials to assess tissue oxygen pressure at the wound site, found it to be ∼110 mm Hg with the administration of 80% oxygen, compared with ∼60 mm Hg in the 30% oxygen control group. The significance of these values is uncertain, and the inclusion of these measurements in the other randomized controlled trials would have added substantially to this body of literature. Even so, we caution that local trauma from the tissue measurement may result in values that do not reliably reflect microvascular conditions.

Surgical site infections develop as the result of complex, multifactorial circumstances. A variety of variables other than
the degree of oxygenation in the macrovascular blood supply affect wound healing, including surgical, anaesthetic, functional, immune, and genetic factors. The promise of a simple physiological intervention to reduce SSIs may be elusive not only for hyperoxia, but for any single intervention. The balance of beneficial and deleterious effects is likely to depend on tissue factors that can vary greatly in a heterogeneous surgical population. In this regard, it is perhaps unsurprising that hyperoxia has not borne out as a singular, sufficient measure to protect against SSI in a broad range of circumstances.

Declaration of interest
None declared.

References
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