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Perioperative Use of High Fraction of Inspired Oxygen: Another Null Result?

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In recent time, the perioperative administration of high fraction of inspired oxygen (F_{IO_2}) has been of great interest to surgeons and anesthesiologists alike. Surgical wounds tend to have lower oxygen tension than normal tissue, and impaired oxygenation is associated with adverse clinical outcomes. Conversely, it has been hypothesized that increasing tissue oxygen tension might exert beneficial effects.[1] This, in turn, can be achieved relatively easy by administering higher F_{IO_2}.[1]

After extensive experimental work, the first large randomized controlled trial was published in 2000.[2] Investigators from Austria, Germany, and the United States collaboratively randomized 500 participants across several trial sites to receive 80% or 30% F_{IO_2} and evaluated wounds for signs of infection. In the 80% group, surgical site infections fell to nearly half of that of the 30% group. However, subsequent trials could not consistently reproduce these results.[3,4] Meanwhile, concerns on potential adverse effects such as atelectasis, respiratory failure, cardiovascular complications, and even mortality due to the use of high F_{IO_2} were raised.[5] In 2016, when both the World Health Organization and the Centers for Disease Control and Prevention independently strongly recommended the use of high perioperative F_{IO_2} for the prevention of surgical site infections, it sparked an academic debate.[6,7] The validity of the evidence for the benefits was challenged, and concerns of potential harms were raised.[8] Not much later, the critical care world was shaken up by a systematic review that indicated liberal oxygen therapy increased mortality in critically ill patients.[9] Although these data were not representative of the perioperative use of high F_{IO_2}, it did fuel the discussion. Since the initial recommendations, new evidence had emerged,[10] and some published trials had come under scrutiny.[11,12] The World Health Organization decided to update its analysis and issued an independent systematic review, specifically on the adverse effect of the use of high F_{IO_2}. The updated analysis did not show a definite beneficial effect of the use of high perioperative F_{IO_2} overall, but there was evidence of a reduction of surgical site infection risk in surgical patients under general anesthesia with tracheal intubation.[13] However, the evidence for this beneficial effect became weaker.[13] The other review, specifically on adverse events, demonstrated no definite signal of harm with 80% F_{IO_2} in adult surgical patients undergoing general anesthesia, and concluded that there is little evidence on safety-related issues to discourage its use in patients undergoing surgery.[14] The guidelines got revised to reflect the new evidence, now suggesting—instead of recommending—the use of high F_{IO_2} perioperatively in patients under general anesthesia with endotracheal intubation, and concluding that additional high-quality trials are needed.[15] The discussion will likely continue.

In this issue of *Anesthesia & Analgesia*, Cohen et al[16] tested an interesting new hypothesis: does the use of high perioperative F_{IO_2} reduce postoperative pain and opioid use? Postoperative pain is common and promotes opioid use. Surgical wounds have high lactate concentration, and the corresponding acidic environment has been associated with pain. Increasing tissue oxygen tension could reduce lactate concentration and possibly the related pain. Use of hyperbaric medicine has shown promising results in the past. The authors conducted a post hoc analysis on a large, single-center, alternating cohort study that assigned 30% (or the lowest F_{IO_2} to maintain hemoglobin saturation at ≥95%) or 80% O_2 to adults undergoing colorectal surgery. Further anesthetic management, such as the use of proactive recruitment manoeuvres or optimization of positive end-expiratory pressure (PEEP), was not controlled. The primary outcome was pain and opioid consumption. After exclusion of patients with regional anesthesia or missing records of pain or opioid administration, a stunning 4702 patients were eligible for analysis who were well balanced across the 2 treatment assignments. No meaningful difference was found in pain scores or opioid use. The authors concluded that supplemental oxygen does not reduce postoperative pain or opioid consumption. Notably, the underlying study with a composite outcome of deep and organ space surgical site infection, healing-related wound complications, and

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mortality as primary end point also found no benefit of the use of high FIO_2.

First and foremost, these authors should be complimented for this enormous effort. With an innovative design, they have managed to allocate an incredible number of patients to 2 different strategies under clinical equipoise, with remarkable balance between the 2 groups. This is an impressive accomplishment.

When we take a closer look at the results, we find that there is no objective measure of tissue or PaO_2, making it impossible to assess whether the protocol used in this setting actually established a difference in cellular oxygen tension. It stands out that the actual administered FIO_2 had a median of 44% (interquartile range, 39–55) in the control group and 81% (interquartile range, 77–82) in the intervention group. This shows that there likely was some overlap between the 2 groups. Although this probably reflects the real-life scenario where caregivers attempt to use the lowest FIO_2 feasible while maintaining hemoglobin saturation at ≥95%, it does risk bias toward the null hypothesis of no effect. But probably more interesting was that it shows that the caregivers involved almost never felt that it was feasible to maintain hemoglobin saturation at ≥95% using 30% FIO_2. When we compare this with data from the 2007 Enigma trial, in which anesthesiologists were given similar instructions in the control group, nearly all the caregivers managed to use 30% FIO_2 (median, 30; interquartile range, 30–32). It is remarkable that the caregivers in the present cohort needed much more inspired oxygen to maintain adequate hemoglobin saturation. It suggests that significant ventilation–perfusion mismatch occurred in some patients, and we can only speculate what interventions clinicians instituted in response. Could administration of high FIO_2 in the intervention group have masked the conditions that led caregivers to intervene in the control group? The available data do not tell. Regretfully, other early studies did not report a measure of spread for the actually administered FIO_2, but it is likely that these values were closer to the Enigma trial than to the present cohort. This difference in oxygen requirement raises the question of what else is different between this cohort and the Enigma trial and other similar studies on this topic.

Since the initial positive findings in 2000, a large shift toward laparoscopic surgery has been made. In the present study, approximately 73% of the procedures were done laparoscopically, while the earlier studies mostly concerned laparotomies. Pneumoperitoneum and Trendelenburg position lead to elevated intra-abdominal pressure and reduced functional residual capacity, with substantial consequences for cardiovascular and respiratory physiology. Even a mild ventilation–perfusion mismatch could require caregivers to increase FIO_2 to maintain adequate hemoglobin saturation. Similarly, high FIO_2 throughout the procedure can mask such subtle occurrences of ventilation–perfusion mismatch that may otherwise have been easily overcome with proactive recruitment maneuvers and a driving pressure–guided institution of PEEP. Fluid infusion and vasopressors used to counteract the hemodynamic consequences of an elevated intra-abdominal pressure could affect microcirculatory perfusion and the actual delivery of oxygen to the tissue one aims to increase by using high FIO_2. Fluid regimen has also markedly changed since the earlier studies. In the early 2000s, patients were typically hydrated aggressively to avoid hypovolemia. Over time, trends have moved from aggressive hydration to restricted fluid regimens and more recently to advanced goal-directed fluid regimens. A restrictive fluid regimen will inevitably require more use of vasopressors to counter intraoperative hypotension. Fluid regimen affects perfusion and thus oxygenation. But, as with the trials on FIO_2, results have been ambiguous when clinical outcomes are concerned.

There are probably many more important differences that we have not addressed here. The point is that anesthesia is a wildly dynamic field with an incredible number of variables at play, most of which affect peripheral oxygenation in some way or form. And whether it is pain, surgical site infection, or something else, when we hypothesize that high FIO_2 might help, we expect it to affect peripheral oxygenation as well. Only the hallmark randomized controlled trial in 2000 actually measured tissue oxygen tension and observed a steep increase when 80% FIO_2 was administered, with comparable oxygen saturation measured by pulse oximetry.[2] For all the subsequent trials, including this cohort, we just do not know whether the increase in FIO_2 accomplished the same. We also do not know whether the increase from 30% to 39%–55% FIO_2 seen in the control group here would have had the same effect as the 80% FIO_2 in the earlier trials, or whether the current conditions that require a higher FIO_2 to maintain hemoglobin saturation at ≥95% here might modify the effect of FIO_2 on the whole. In hindsight, setting a goal for tissue or PaO_2 rather than a static measure like high FIO_2 might have led to more consistent and reliable results.

The present study indicates that 80% FIO_2 compared to the lowest feasible FIO_2 under the perioperative conditions at this trial site does not meaningfully change clinical outcomes. But it also indicates that perioperative care has changed substantially since the early encouraging results. If the premise of improved outcomes through improved oxygenation is pursued further, a broadened understanding of tissue oxygen tension during anesthesia is needed. Future studies should include measurement of tissue and PaO_2, standardized ventilation management with proactive recruitment maneuvers and a driving pressure–guided institution of PEEP, as well as pain, fluid, and temperature management protocols.

DISCLOSURES

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Contribution: This author helped draft the manuscript.
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REFERENCES

1. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg*. 1997;132:997–1004.
2. Greif R, Akça O, Horn EP, Kurz A, Sessler DI; Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 2000;342:161–167.
3. Meyhoff CS, Wetterslev J, Jorgensen LN, et al; PROXI Trial Group. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA*. 2009;302:1543–1550.

4. Belda FJ, Aguilera L, García de la Asunción J, et al; Spanish Reduccion de la Tasa de Infeccion Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA.* 2005;294:2035–2042.
5. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS; PROXI Trial Group. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg.* 2012;115:849–854.
6. World Health Organization. *Global Guidelines for the Prevention of Surgical Site Infection*. Geneva, Switzerland: World Health Organization; 2016.
7. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg.* 2017;152:784–791.
8. Hedenstierna G, Perchiazzi G, Meyhoff CS, Larsson A. Who can make sense of the WHO guidelines to prevent surgical site infection? *Anesthesiology.* 2017;126:771–773.
9. Chu DK, Kim LH, Young PJ, 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;391:1693–1705.
10. Kurz A, Fleischmann E, Sessler DI, Buggy DJ, Apfel C, Akça O; Factorial Trial Investigators. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomized trial‡. *Br J Anaesth.* 2015;115:434–443.
11. Schietroma M, Cecilia EM, Sista F, Carlei F, Pessia B, Amicucci G. High-concentration supplemental perioperative oxygen and surgical site infection following elective colorectal surgery for rectal cancer: a prospective, randomized, double-blind, controlled, single-site trial. *Am J Surg.* 2014;208:719–726.
12. Schietroma M, Cecilia EM, Carlei F, et al. Prevention of anastomotic leakage after total gastrectomy with perioperative supplemental oxygen administration: a prospective randomized, double-blind, controlled, single-center trial. *Ann Surg Oncol.* 2013;20:1584–1590.
13. de Jonge S, Egger M, Latif A, 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;122:325–334.
14. Mattishent K, Thavarajah M, Sinha A, et al. Safety of 80% vs 30-35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis. *Br J Anaesth.* 2019;122:311–324.
15. World Health Organization. *Global Guidelines for the Prevention of Surgical Site Infection*, 2nd ed. Geneva, Switzerland: World Health Organization; 2018.
16. Cohen B, Ahuja S, Schacham YN, et al. Intraoperative hyperoxia does not reduce postoperative pain: subanalysis of an alternating cohort trial. *Anesth Analg*. 2019;128:1160–1166.