Review Article

Setting intraoperative fraction of inspired oxygen

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Abstract: Each year, millions of patients undergo surgery under general anaesthesia. Oxygen, the most ubiquitous drug used in the operative setting, is often titrated to the anaesthesiologist preference. The choice of a high inspired fraction of inspired oxygen (FiO_2) is commonplace. Safety criteria along with a debatable effect on a decrease in surgical site infection (SSI) are the potential reasons to justify a high FiO_2 usage. Based on the latter, several organizations such as the World Health Organization (WHO) or Centers for Disease Control (CDC) have issued recommendations to keep high FiO_2 during surgery and the immediate postoperative period. In this article, we will review the evidence behind these beneficial effects and several potential side effects of a high FiO_2 intraoperative strategy.

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Introduction

Each year, millions of patients undergo surgery under general anaesthesia (1). Oxygen, the most ubiquitous drug used in the operative setting, is often not titrated to any particular effect, but to the anaesthesiologist's preference and usual practice. The choice of a high inspired fraction of inspired oxygen (FiO_2) is commonplace in the operating room (2) and, in general, differs significantly from the intensive care setting. Safety criteria along with a debatable effect on a decrease in surgical site infection (SSI) are the potential reasons to justify a high FiO_2 usage. Based on the latter, several organizations such as the World Health Organization (WHO) (3) or Centers for Disease Control (CDC) (4) have issued recommendations to keep high FiO_2 during surgery and the immediate postoperative period. In this article, we will review the evidence behind these beneficial effects and several potential side effects of a high FiO_2 intraoperative strategy.

Safety criteria to advocate for a high FiO_2 usage during anaesthesia

At induction of anaesthesia, using high FiO_2 increases alveolar oxygen concentration which prolongs time-to-hypoxemia onset after apnea. The goal of preoxygenation is to achieve an expired oxygen concentration above 0.9, which is usually achieved after 3 to 5 min. In a healthy adult, this will provide an apnea time around 8 to 10 min. In the setting of an unanticipated difficult airway this could provide of invaluable help. Several populations known to present with rapid desaturation after apnea, such as children, obese patients and pregnant women, may specially benefit from this intervention (5,6). National guidelines often recommend setting a high FiO_2 before induction of anaesthesia and during bag-mask ventilation. Continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) are interesting options to improve the efficacy of preoxygenation and have

been tested in different scenarios (7-9).

Intraoperative and postoperative

SSI is one of the commonest complications after surgery with incidences varying depending on the type of surgery. A recent global report found SSIs to occur in 9% of all gastrointestinal surgeries in high-income countries whereas the incidence doubled when only surgery considering to be dirty was analysed. When low-income countries were studied, SSIs were up to 40% (10). SSIs have been associated with severe complications thereafter, such as anastomotic leak and sepsis and septic shock. SSIs prolong hospital length of stay as well as increase health-care costs (11-14).

Peripheral tissue hypoxia at the surgical wound might impair the innate immune system to cope with bacteria migrating and replicating inside the tissues. Oxygen is an essential element for neutrophils since this cell mediates its primary effect through an oxidative mechanism (15,16). Hence, increasing oxygen pressure at the tissue level (PtO_2) could potentially provide useful to reduce SSIs. Oxygen transport depends on both cardiac output and arterial oxygen content; which is a function of the haemoglobin level and its saturation and, also, of the dissolved content of oxygen (17). Once accomplishing a stable cardiac output and an appropriate haemoglobin level with saturation above 97%, the increase in PtO_2 will come from the increase in arterial pressure of oxygen (PaO_2). Hence, a plausible approach to increase PtO_2 is to achieve supraphysiologic PaO_2 by means of increasing FiO_2 (18). This strategy has been a matter of debate for years with several randomized controlled trials (RCT) aiming to answer this question. Greif *et al.*, was the first to show on a 500-patient sample undergoing open abdominal surgery that FiO_2 0.8 as compared to FiO_2 0.3 in the intraoperative and early postoperative period reduced SSIs by more than 50% (19). Later, several authors using similar designs found comparable results (20,21). However, additional RCTs did not replicate these findings, including the largest RCT performed in this field to date, which included almost 1,400 patients (22-26). A meta-analysis carried out by the WHO that included 15 trials found a significant effect for a high FiO_2 in decreasing SSIs which led this organisation to recommend the usage of FiO_2 0.8 during surgery and the first few hours in the postoperative period (3). Importantly, some of the previous articles suggesting a beneficial effect of a high FiO_2 strategy, that were included in this meta-analysis, have been retracted in the last few years (27). Since then, additional meta-analysis not including these articles have found conflicting results of setting a FiO_2 0.8 as compared to a FiO_2 0.3–0.35 (28,29). For these reasons, the WHO recently updated their recommendations; while keeping the advice to maintain FiO_2 at 0.8, the strength of the recommendation was weakened from strong to conditional (30).

Beyond the usual differences in designs and outcomes between trials that often makes a straightforward comparison difficult, we would like to highlight that a non-homogeneous ventilatory strategy in the previous studies might have affected the efficacy of FiO_2. Kurz *et al.*, noticed important differences in PaO_2 in the group allocated to high FiO_2 that these authors consider related to different PEEP strategies (24). Of note, only the first trial conducted by Greif *et al.* measured PtO_2; hence we cannot be confident to state that the high FiO_2 group in these studies had shown a better oxygen delivery (19). It is also noteworthy that hypoxemia (even small deviations from 100 mmHg) was very uncommon in these studies making impossible to draw conclusions whether avoiding hypoxemia could be more important that increasing PaO_2 in already normoxemic patients. Observational data has also shown that most of the patients (more than 97%) under general anaesthesia shows blood oxygen saturation (SpO_2) ≥96% (2). In another line of thought, it is also remarkable that the vast majority of patients enrolled in these studies underwent abdominal surgery via an open approach. There is nowadays extensive research showing that laparoscopic or minimal invasive surgery reduces SSIs (31-34) and the ongoing growth of these approaches might make the small, if ever present, effect of a high FiO_2 undetectable.

Importantly, oxygen as any other drug has the potential to cause adverse effects. However, most trials that did not show a beneficial effect of a high FiO_2 strategy did not report more complications (22-26) as neither meta-analysis did (35).

Potential risks associated with a high FiO_2 strategy

Respiratory

During anaesthesia the loss of diaphragmatic tone leads to a decrease in functional residual capacity (FRC) that moves the lung volume closer to residual volume. This could lead to end-expiratory lung volume (EELV), which

is the equivalent to FRC under mechanical ventilation, to become smaller than the closing capacity. Also, compressive atelectasis can ensue which cause airway to collapse. All of this may produce dependent lung portions to become closed or partially closed. In this situation, gas inside the alveoli pass to the circulation but cannot be replaced with ventilation leading to dependent lung collapse. Oxygen through its greater diffusion capacity as compared to nitrogen might favour this situation to happen; which, in its turn, could lead to hypoxemia and respiratory failure after extubation (36). However, physiological data has shown that when FiO_2 is set at 0.8 or below, resorption atelectasis do not increase significantly (37). Also, use of positive end-expiratory pressure (PEEP) during mechanical ventilation might minimize this effect. In line with these data, most trials targeting a high FiO_2 did not report an increase in respiratory complications after the use of a high FiO_2 during surgery.

Moreover, a high alveolar oxygen concentration could, through an increase in oxidative stress at the lung, be associated with hyperoxic acute lung injury. In the past, there has been extensive research performed in animals showing that breathing high oxygen concentrations for a prolonged period leads to lung injury. This research, in general, conducted in healthy animals showed that breathing FiO_2 ≥0.8 for several days cause pulmonary damage in a wide variety of species. Also, as the concentration decreases, the time needed to cause harm increases markedly (38). From the observations mentioned, it seems that hyperoxic acute lung injury occurs after inhalation of high FiO_2 that occurs for days or even weeks; which is a condition not met in anaesthesia in the operating room. Notwithstanding, there is some evidence to suggest that already injured lungs or those ventilated in a nonprotective way can be more susceptible to high FiO_2 exposure; even at concentrations around 0.6 (39). Although, it is unlikely that a short term exposure to a high FiO_2 will be detrimental for the lung, we should be aware that oxygen is a potential toxic element when used at high doses and could potentially work as a "second-hit" in situations where lungs are at risk of presenting further damage such as in septic shock or acute respiratory distress syndrome (ARDS).

Neurologic

Oxygen is known to be capable of causing acute neurologic toxicity when used at hyperbaric conditions such as those experienced during scuba diving. Thresholds for acute neurologic injury has been set around 1.3–1.6 bar (40) which is a condition never met in a normobaric situation. Hence, oxygen neurologic toxicity is not a concern in the intraoperative setting.

Vascular

There is concern that hyperoxia could contribute to myocardial vasoconstriction through a competing mechanism with nitric oxide or to an increase in reactive oxygen species (41). In 2015, a multicentre trial where 441 patients with ST-elevation myocardial infarction was published. In this study patients with an SpO_2 >94% were randomized to receive 8 L/min of oxygen or no supplemental oxygen on arrival of paramedics and up to transfer to the cardiac care unit. The patients that received supplemental oxygen had an increased rate of recurrent myocardial infarction as well as the frequency of cardiac arrhythmias and showed a larger infarct size at 6 months on magnetic resonance imaging (42). Evidence coming from the stroke literature is conflicting with both observational studies and small trials showing no difference with supplementation, detrimental effects or even short-lived beneficial outcomes (43). However, an RCT performed in the intensive care unit compared the effect of two FiO_2 strategies on the outcome of ventilated patients. The liberal approach consisted of allowing SpO_2 ≥97% and PaO_2 to increase up to 150 mmHg while the conservative approach targeted SpO_2 in the 94–98% range with PaO_2 between 70 and 100 mmHg. In this study, the conservative approach showed an absolute 8.6% mortality reduction (from an overall 20.2% mortality in the liberal group) with fewer episodes of shock, liver failure and bloodstream infections (44). However, literature coming from cardiac surgery does not support the notion that high intraoperative FiO_2 is associated with an increase rate of complications. (45,46). A large RCT that randomized surgical patients to high FiO_2 *vs.* FiO_2 0.3 will probably present results soon regarding the effect of this strategy not only on SSIs but on vascular complications and, also, renal failure (47).

Conclusions

After several decades and many studies trying to assess whether a high FiO_2 strategy would result protective in terms of SSIs reduction, the available data is not conclusive. In the past century, investigators showed that increasing

tissue oxygen availability at the time of surgery would reduce local complications. However, increasing FiO_2 does not necessarily translate immediately into a PtO_2 rise since oxygen delivery is affected upon several factors such as the haemoglobin level and the cardiac output. Also, ventilatory management affects the oxygen gradient between the alveoli and the circulation. Kurz *et al.* demonstrated that in their high-FiO_2 group, PaO_2 would differ markedly between subjects depending on the level of PEEP used, an observation also evident from our clinical practice. Since, the study by Greif *et al.* was the only one to measure PtO_2, we cannot be certain that the intervention in the studies was effective to increase oxygen availability at the tissues to a level to be effective in reducing SSIs. This observation underscores the importance of ventilatory management in assessing the interaction with FiO_2 to maximize PaO_2 and PtO_2. In this line, a large RCT studying the effect of a high FiO_2 approach, using a standardized open lung strategy to all patients, will soon show results (47). Also, most of these studies were performed more than a decade ago and a majority of patients enrolled were operated with an open approach. Given the growth of the laparoscopic techniques and the reduction in SSIs demonstrated with them, the positive effects observed by a high intraoperative FiO_2 might dilute even more.

On the other hand, adverse effects of a high FiO_2 strategy in the intraoperative setting seem not to be relevant. Even though, literature coming from the intensive care suggest hyperoxemia is associated with complications and increased mortality in wide populations of critical care patients, the studies performed in the operating room have not shown this relationship. Importantly, research done in cardiac surgery did not show an increase in myocardial damage or renal failure in subjects allocated to a high-FiO_2 strategy. Although the differences in the outcomes between the studies could possibly be explained by dissimilar populations between the surgical setting and the critical care environment as well as a very different exposition time to high FiO_2 between one setting and the other; we should all be aware that oxygen as any other drug has the potential to cause side effects when used in a large concentration for a long period of time.

At this time point, we feel the literature is conclusive in acknowledging the importance of keeping an adequate oxygen delivery to tissues in order avoid complications, and particularly SSIs. To maintain an adequate oxygenation level with the use of a careful ventilatory strategy, to keep the cardiac output stable, to avoid severe anaemia, to prevent patients from developing hypothermia, or to keep blood glucose levels below 200 mg/dL are all essential factors in any anaesthetist's good intraoperative management. Regarding FiO_2 supplementation, studies, however, have not been conclusive to recommend a high-FiO_2 strategy to all patients undergoing major surgery but have shown that this approach seems safe when restricted to the operating theatre and the first hours after surgery. In settings with limited resources and where SSIs incidence is very high, or in situations where keeping oxygen delivery might be difficult such as in the case of acute anaemia or patients who refuse transfusion, a high-FiO_2 strategy could prove useful to reduce SSIs; however, evidence of benefit in this subgroup is lacking.

In conclusion, the research published so far does not support the use to high-FiO_2 during surgery to all subjects undergoing major surgery. New evidence coming from a large RCT will soon shed light on this field.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372:139-44.
2. LAS VEGAS investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries. Eur J Anaesthesiol 2017;34:492-507.
3. Allegranzi B, Zayed B, Bischoff P, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis

2016;16:e288-303.
4. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg 2017;152:784-91.
5. Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: Physiologic Basis, Benefits, and Potential Risks. Anesth Analg 2017;124:507-17.
6. Campbell IT, Beatty PC. Monitoring preoxygenation. Br J Anaesth 1994;72:3-4.
7. Rusca M, Proietti S, Schnyder P, et al. Prevention of atelectasis formation during induction of general anesthesia. Anesth Analg 2003;97:1835-9.
8. El-Khatib MF, Kanazi G, Baraka AS. Noninvasive bilevel positive airway pressure for preoxygenation of the critically ill morbidly obese patient. Can J Anaesth 2007;54:744-7.
9. Jaber S, Monnin M, Girard M, et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med 2016;42:1877-87.
10. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. Lancet Infect Dis 2018;18:516-25.
11. Michard F, Mountford WK, Krukas MR, et al. Potential return on investment for implementation of perioperative goal-directed fluid therapy in major surgery: a nationwide database study. Perioper Med (Lond) 2015;4:11.
12. Cohen ME, Bilimoria KY, Ko CY, et al. Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. J Am Coll Surg 2009;208:1009-16.
13. Haley RW, Culver DH, Morgan WM, et al. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. Am J Epidemiol 1985;121:206-15.
14. Ferrando C, Belda J, Soro M. Perioperative hyperoxia: Myths and realities. Rev Esp Anestesiol Reanim 2018;65:183-7.
15. Babior BM. Oxygen-Dependent Microbial Killing by Phagocytes. N Engl J Med 1978;298:659-68.
16. Allen DB, Maguire JJ, Mahdavian M, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. Arch Surg 1997;132:991-6.
17. Dunn JOC, Mythen MG, Grocott MP. Physiology of oxygen transport. BJA Education 2016;16:341-8.
18. Sessler DI. Non-pharmacologic prevention of surgical wound infection. Anesthesiol Clin 2006;24:279-97.
19. Greif R, Akça O, Horn EP, et al. Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161-7.
20. Belda FJ, Aguilera L, García de la Asunción J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005;294:2035-42.
21. Bickel A. Perioperative Hyperoxygenation and Wound Site Infection Following Surgery for Acute Appendicitis. Arch Surg 2011;146:464.
22. Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of High Perioperative Oxygen Fraction on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery. JAMA 2009;302:1543.
23. Thibon P, Borgey F, Boutreux S, et al. Effect of perioperative oxygen supplementation on 30-day surgical site infection rate in abdominal, gynecologic, and breast surgery: the ISO2 randomized controlled trial. Anesthesiology 2012;117:504-11.
24. Kurz A, Fleischmann E, Sessler DI, et al. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomized trial‡. Br J Anaesth 2015;115:434-43.
25. Pryor KO, Fahey TJ, Lien CA, et al. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. JAMA 2004;291:79-87.
26. Mayzler O, Weksler N, Domchik S, et al. Does supplemental perioperative oxygen administration reduce the incidence of wound infection in elective colorectal surgery? Minerva Anestesiol 2005;71:21-5.
27. Myles PS, Carlisle JB, Scarr B. Evidence for compromised data integrity in studies of liberal peri-operative inspired oxygen. Anaesthesia 2019;74:573-84.
28. Cohen B, Schacham YN, Ruetzler K, et al. Effect of intraoperative hyperoxia on the incidence of surgical site infections: a meta-analysis. Br J Anaesth 2018;120:1176-86.
29. 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;122:325-34.
30. WHO. Global guidelines for the prevention of surgical site infection. second edition. 2018.
31. Aimaq R, Akopian G, Kaufman HS. Surgical site infection

rates in laparoscopic versus open colorectal surgery. Am Surg 2011;77:1290-4.
32. Gandaglia G, Ghani KR, Soo A, et al. Effect of Minimally Invasive Surgery on the Risk for Surgical Site Infections. JAMA Surg 2014;149:1039.
33. Xiao Y, Shi G, Zhang J, et al. Surgical site infection after laparoscopic and open appendectomy: a multicenter large consecutive cohort study. Surg Endosc 2015;29:1384-93.
34. Kagawa Y, Yamada D, Yamasaki M, et al. The association between the increased performance of laparoscopic colon surgery and a reduced risk of surgical site infection. Surg Today 2019;49:474-81.
35. 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;122:311-24.
36. Magnusson L, Spahn DR. New concepts of atelectasis during general anaesthesia. Br J Anaesth 2003;91:61-72.
37. Akça O, Podolsky A, Eisenhuber E, et al. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. Anesthesiology 1999;91:991-8.
38. Kallet RH, Matthay MA. Hyperoxic Acute Lung Injury. Respir Care 2013;58:123-41.
39. Aggarwal NR, Brower RG. Targeting Normoxemia in Acute Respiratory Distress Syndrome May Cause Worse Short-Term Outcomes because of Oxygen Toxicity. Ann Am Thorac Soc 2014;11:1449-53.
40. Wingelaar TT, van Ooij P-JAM, van Hulst RA. Oxygen Toxicity and Special Operations Forces Diving: Hidden and Dangerous. Front Psychol 2017;8:1263.
41. Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J 2009;158:371-7.
42. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 2015;131:2143-50.
43. Vincent JL, Taccone FS, He X. Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke: The Importance of Individualized Oxygen Therapy in Critically Ill Patients. Can Respir J 2017;2017:2834956.
44. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. JAMA 2016;316:1583.
45. Smit B, Smulders YM, de Waard MC, et al. Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. Crit Care 2016;20:55.
46. McGuinness SP, Parke RL, Drummond K, et al. A Multicenter, Randomized, Controlled Phase IIb Trial of Avoidance of Hyperoxemia during Cardiopulmonary Bypass. Anesthesiology 2016;125:465-73.
47. Ferrando C, Soro M, Unzueta C, et al. Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial. BMJ Open 2017;7:e016765.

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