Perioperative Hyperoxia

The Debate Is Only Getting Started

In this issue of Anesthesiology, Stæhr et al. report the lack of effect of perioperative hyperoxia on preventing surgical site infection (SSI) in obese patients undergoing laparotomy. The study was a secondary analysis of data from the PROXI Trial, a Danish multicenter study of 1,400 patients undergoing elective or emergency laparotomy who were randomized to receive a 30% or 80% oxygen concentration intraoperatively and for the first 2 h after surgery. Although no significant reduction in the frequency of SSI was observed in the high-concentration group in that trial, it was hypothesized that the results for the subpopulation of 213 obese patients (body mass index $\geq 30$ kg/m$^2$, 15% of the sample) might be different. However, on reanalysis the researchers again found no significant differences in the rates of SSI or pulmonary complications.

Surgical site infection, which accounts for 15–20% of all healthcare-associated infections, is the second most common preventable adverse outcome of major surgery. The incidence of SSI, which differs according to surgical procedure, is highest for gastrointestinal interventions. If we are to decrease the SSI rates in the various surgical settings and attenuate the consequences, it will be necessary to identify risk factors as a first step. Age, duration of surgery, hypoalbuminemia, obesity, diabetes mellitus, and a history of chronic obstructive pulmonary disease are some of the predictors that have been linked with SSI.

Obesity is associated with a higher incidence of SSI. Glance et al. recently studied a population of 310,208 patients in the American College of Surgeons National Surgical Quality Improvement Program database, more than 95,000 of whom were overweight. Obese and morbidly obese patients with metabolic syndrome (obesity, hypertension, and diabetes), who accounted for 19% of all the obese patients in the study, had higher risk of postoperative complications, including death and SSI, in comparison with normal-weight and obese patients without metabolic syndrome. In addition, percentage of body fat and thickness of subcutaneous fat have been shown to be better predictors of SSI than body mass index, suggesting that obesity is not a homogeneous clinical state and body mass index may be too simplistic a measure for this complex illness. In other words, individuals classified as obese may be more or less healthy and have different levels of risk.

In recent years, interest has grown in identifying factors amenable to management to reduce the risk of SSI, and anesthesiologists may have partial control over some of them. Measures such as the avoidance of hypothermia and the careful timing and selection of antibiotics seem to be effective in preventing SSI.

The rationale for proposing hyperoxia as another manageable factor for preventing SSI is well established. Neutrophils safeguard against infection through nonspecific phagocytosis and elimination of bacteria from wounds; the oxygen tension in subcutaneous tissue is critical for these functions. Tissue oxygen tension and concentration have been shown to predict SSI after colorectal surgery, and supplemental oxygen (e.g., 80%) can double oxygen partial pressure in tissue. In vitro studies have shown that hyperoxia exerts significant influence on multiple cellular and immune system parameters, improving the functional capacity of the innate immune response as reflected by increasing concentrations of reactive oxygen species, a major component of the bactericidal defense. Adequate wound oxygen tension is also important in the development of collagen and epithelium required for healing. Hyperoxia increases the availability of molecular oxygen to tissues by increasing oxygen dissolved in plasma and enhancing the driving force between capillary blood and cells. Achieving a subcutaneous oxygen tension greater than 90 mmHg seems to protect against infection, and at least 40 mmHg would be needed to support the leukocyte-mediated oxidative burst and collagen formation. Good capillary perfusion of tissue also determines cell oxygenation, and helpful actions that can be managed by anesthesiologists are fluid replacement and the avoidance of vasoconstriction triggered by activation of the sympathetic nervous system by hypothermia and pain. However, all actions intended to increase cell oxygen tension can be offset if tissue perfusion is compromised (e.g., in diabetes or peripheral vascular disease) or when the oxygen pressure gradient along the axial capillary drops rapidly.

The results of the clinical translation of this rationale, in controlled trials testing perioperative hyperoxia, have been mixed. Two randomized trials comparing 30% and 80% oxygen in a total of almost 800 patients undergoing colorectal surgery reported significant reductions in the rate of SSI. A large trial to test the effect of nitrous oxide on events after major surgery indirectly compared high (80%) and low (30%) oxygen concentrations and found significantly fewer cases of SSI in patients breathing the high concentration. In contrast, 165 patients undergoing major

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abdominal surgery, including laparoscopically assisted procedures, were randomized to breathe 35% or 80% oxygen, and no improvement in SSI outcome was observed. Finally, the multicenter PROXI Trial likewise found no significant reduction in risk of SSI with hyperoxia; however, the study included many different elective and emergency surgical procedures, ranging from high-risk colorectal interventions (fewer than 50% of all patients) to cholecystectomies, appendectomies, and hernia repair. This heterogeneity could partly explain the negative findings.

The secondary analysis of data for the PROXI Trial’s high-risk subgroup of obese patients in this issue is therefore welcome. It was hypothesized that the subcutaneous oxygen tension might be reduced in this subpopulation because of their anatomic, histologic, functional, and immune status. We know that in obese patients tissue oxygen tension is significantly increased when 80% oxygen is given, favoring the defense mechanisms against an SSI. However, the authors observed no reduction in the incidence of SSI. Two sampling characteristics could have created bias leading to this negative result. First, the mean body mass index of the obese patients in this trial was relatively low (33.5 kg/m²), and hypertension was present in fewer than half the patients, suggesting that a large proportion did not have metabolic syndrome and probably had less risk. Second, the patients had undergone a large variety of procedures, and only 45% were operations such as colorectal surgery, which is associated with high risk for SSI.

Thus, the issue of a clinical role for hyperoxia remains unsettled. Should we routinely administer high oxygen concentration perioperatively in the hope of reducing the risk of SSI? This intervention is attractive because oxygen therapy does not significantly increase costs, and the potential benefits might be great. But SSIs develop as the result of very complex circumstances, and prevention does not appear to be possible by taking a single step because a variety of other surgical, anesthetic, functional, and immune factors also play important roles. Even genetic factors seem to increase risk for severe infections. Our poor understanding of those factors probably explains the conflicting results of trials to date. The answer to the question posed above seems to be that hyperoxia should not be provided routinely and individualized clinical vigilance is essential. Probably in some patients who are theoretically at high risk of infection (e.g., in colorectal surgery) but whose tissue perfusion is well preserved, hyperoxia with 80% oxygen concentration may be beneficial. Additional research with high-risk patients undergoing high-risk procedures is needed. New studies on general populations probably will yield negative results because the beneficial effect of hyperoxia by itself can be marginal, or at least not comparable to antibiotic prophylaxis. Thus, to reduce risk of SSI, we would argue in favor of a multimodal approach, including several surgical and anesthetic factors amenable to management. In such an approach, hyperoxia might well be one of the tools to select.

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References