Effect of High Perioperative Oxygen Supplementation on Surgical Site Infections

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Over the past 15 years, several randomized controlled trials, long-term follow-up studies, meta-analyses, and editorials have been published in regard to the effect of a high fraction of inspired oxygen concentration (FiO2) during the perioperative period on the incidence of surgical site infections. Although the evidence is not uniformly favorable for all types of surgeries, a beneficial association of 80% FiO2 has been documented among open abdominal procedures, especially colorectal surgeries.

Keywords. perioperative; oxygen supplementation; surgical site infection; colorectal surgeries; abdominal surgeries.

Since 2000, several trials have been published on the use of high fraction of inspired oxygen concentration (FiO2) during the perioperative period and its potential association with lower rates of surgical site infections (SSIs). These studies include randomized controlled trials (RCTs), meta-analyses, and long-term survival follow-up of the original cohorts.

Also during the past decade, hospital-acquired infections have received increasing visibility not only among the US government and hospitals, but also among the general public [1]. SSIs have been previously described as the most frequent hospital-acquired infections, with colon surgeries constituting the procedures with the highest incidence of infections (range, 3.49%–13.78%) [2, 3].

During 2006–2008, there were 849,659 surgeries and 16,147 SSIs reported to the National Healthcare Safety Network (NHSN) [4]. In 2007, the cost of inpatient hospital services associated with these infections was in the range of $3.45–$10.07 billion [5]. Furthermore, reporting of monthly surgical infection rates to NHSN is now required by the Centers for Medicare and Medicaid for certain surgeries, such as colon procedures and abdominal hysterectomies. Therefore, interventions to decrease SSI rates are urgently needed. We aim to update the infectious diseases community on the data that have accumulated during the past decade and a half in regard to the use of high perioperative FiO2 and its effect on SSIs and mortality.

RATIONALE FOR USE OF HIGH FiO2

Hypoxic wounds not only have a slower rate of healing but also a higher risk of developing infections proportional to the degree of tissue hypoxia [6]. Oxygen at the wound site is believed to be associated with heightened bactericidal activity of neutrophils through increased oxidative killing [7, 8]. Additionally, the activity of antibiotics might be enhanced at higher levels of oxygen [9].

Peripheral tissues are oxygenated via movement of oxygen down a partial pressure gradient. Oxygen is delivered via capillary flow, and anything that limits blood flow, decreases arterial oxygen content, or lessens movement of oxygen along its gradient can negatively impact tissue oxygenation. Surgical wounds can be hypoxic due to 2 main factors: (1) poor systemic oxygen delivery, which is determined by both the cardiac output and the arterial oxygen content, or by (2) locally
interrupted blood flow due to surgical trauma to blood vessels or edema (third spacing) causing increased intercapillary distance. These 2 main factors are impacted by many others, including vasoconstriction—caused by hypothermia, hypovolemia, or pain, all of which are common during surgery—decreased cardiac function (eg, ischemia, failure), decreased oxygen content (eg, hypoxemia, significant anemia), and type and amount of fluid resuscitation during the perioperative period. Therefore, the rationale of hyperoxygenating a patient consists of increasing partial oxygen pressures at the wound site, increasing neutrophil activity with an ultimate decrease in SSIs.

Randomized Controlled Trials

Open Abdominal Procedures

The first RCT on the topic was published in 2000 by Grief and colleagues [10]. This study compared the effects of minimal recommended oxygen supplementation under anesthesia (an FiO2 of 30%) vs 80% FiO2 on the rates of SSIs among patients undergoing elective open colorectal resections. As was done in most of the RCTs that we will review, patients with evidence of infection at the time of surgery were excluded from the study. A total of 13 SSIs were identified in the intervention group (13/250 [5.2%]) and 28 among the controls (28/250 [11.2%]; P = .01). Further details on inclusion criteria, interventions, SSI definitions, and outcomes on each of the RCTs are shown in Tables 1 and 2.

In 2004, Pryor and colleagues published a study evaluating the effect of oxygen in preventing SSIs among patients undergoing major abdominal procedures [11]. Although this study was not performed solely among colorectal surgeries, approximately two-thirds of cases in each group were surgeries on the large bowel. Importantly, close to half of the intraoperative pathology specimens were cancer related. The intervention and control groups received 80% and 35% FiO2, respectively. The SSI rate in the intervention group was 25% (20/80) and 11.3% (9/80) among controls (P = .02). This is the only study that found a statistically significant difference against the intervention. This unique finding has been a source of debate on the efficacy of perioperative oxygen supplementation since its publication; hypotheses explaining this result include the higher prevalence of obesity, blood loss, and crystalloid infusion among the high oxygen group, potential lapses in regards to blinding, and ascertainment of the outcomes using chart reviews rather than physical evaluations by study investigators [12, 21, 22].

In 2005, Belda and collaborators performed a multicenter RCT across 14 Spanish hospitals evaluating 80% vs 30% FiO2 among patients undergoing elective colorectal resections [12]. Twenty-two patients were diagnosed with SSIs in the intervention group (22/148 [14.9%]) compared to 35 among controls (35/143 [24.4%]; P = .04).

The PROXI trial published in 2009 by Meyhoff and colleagues was one of the 2 largest trials on this topic [14]. It was performed across 14 Danish hospitals and compared 80% vs 30% FiO2 on the development of SSIs. A total of 1386 patients were included, with about half of the cases being colorectal procedures and the remaining ones a mixture of gynecological procedures, small-bowel interventions, and appendectomies. SSIs occurred in 131 of the 685 patients in the intervention (19.1%) and 141 of the 701 patients in the control group (20.1%; P = .64). Therefore, this large RCT failed to show a difference between the groups. Reasons postulated for this lack of difference include conservative volume administration, absence of preoperative bowel preparation, and the lack of standardization of normothermia among the study participants [23, 24]. There was a subsequent subgroup analysis of this trial on obese patients (body mass index ≥30 kg/m²) [25]. In this subgroup, oxygen supplementation failed to show a difference in the incidence of SSIs, with rates of 31% (32/102) and 30% (29/111) among the high and low oxygen supplementation groups, respectively (P = .4).

Bickel and colleagues evaluated oxygen supplementation among 210 patients requiring open appendectomies due to acute appendicitis [15]. The intervention group received 80% oxygen and the control group was supplemented with 30% oxygen. The authors found a SSI rate of 5.6% (6/107) in the intervention group and 13.6% (14/103) in the control group (P = .04), in favor of high oxygen supplementation.

Mixed Cases and Nonabdominal Surgeries (Excluding Cesarean Deliveries)

The largest study on this topic is the ENIGMA trial, which encompassed 2012 patients across 19 sites worldwide [16]. Interestingly, this study aimed to compare the benefits of avoiding a nitrous oxide–based anesthetic on the onset of SSIs. One of the groups received nitrous oxide–free anesthesia (80% oxygen plus 20% nitrogen) and the other one received a nitrous oxide–based anesthesia (30% oxygen plus 70% nitrous oxide). Their primary outcomes were length of stay and rates of SSIs. Thus, this study did not target the effect of high oxygen supplementation but rather the effect of nitrous oxide, indirectly evaluating high vs low oxygen supplementation. Inclusion criteria consisted of requiring general anesthesia for at least 2 hours and an in-hospital stay for ≥ 3 days. Only 15% of patients had colorectal surgeries, whereas the rest were a mixture of other general surgeries, neurosurgeries, urologic surgeries, and orthopedic surgeries, among others. Wound infections were identified in 7.7% of patients (77/997) assigned to the high oxygen/nitrous oxide–free group vs 10% of patients (106/1015) who received the 30% oxygen/nitrous oxide–based mixture (P = .036). These results favor the use of high oxygen and/or nitrous oxide–free anesthesia instead of a high nitrous oxide mixture with an FiO2 of 30%. The conclusions we can reach from ENIGMA in regard to the use of
<table>
<thead>
<tr>
<th>Author</th>
<th>Oxygen Fractions (High vs Low Oxygen Groups)</th>
<th>Duration of Oxygen Supplementation</th>
<th>Surgical Site Infection Definition</th>
<th>Time of Follow-up (After Index Surgery)</th>
<th>Method for Ascertainment Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open abdominal surgeries</strong></td>
<td></td>
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<tr>
<td>Grief et al, 2000 [10]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>Presence of purulent drainage from the surgical incision with a positive wound culture</td>
<td>15 d</td>
<td>Physicians, blinded to group allocation and not members of the operative surgical teams, evaluated wounds daily while inpatient and then again in outpatient clinic</td>
<td></td>
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<tr>
<td>Pryor et al, 2004 [11]</td>
<td>80% vs 35% Surgery plus 2 postoperative hours</td>
<td>Documented diagnosis of surgical site infection by the managing team with a subsequent action (such as initiation of antibiotics) and the presence of objective measurements of infection (eg, leukocytosis, fever)</td>
<td>14 d</td>
<td>Review of inpatient and outpatient medical records by investigator blinded to randomization</td>
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<tr>
<td>Belda et al, 2005 [12]</td>
<td>80% vs 30% Surgery plus 6 postoperative hours</td>
<td>CDC criteria</td>
<td>14 d</td>
<td>Daily wound evaluations by surgeons blinded to group allocation (inpatient)</td>
<td></td>
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<tr>
<td>Mayzler et al, 2005 [13]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>Appearance of erythema with local pain and drainage of fluid or purulent secretion</td>
<td>30 d</td>
<td>Daily wound evaluations by surgeons blinded to group allocation (inpatient) and again in the outpatient clinic</td>
<td></td>
</tr>
<tr>
<td>Meyhoff et al, 2009 (PROXI trial) [14]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>CDC criteria</td>
<td>14 d</td>
<td>Surgical investigators blinded to group allocation performed daily wound evaluations daily and then in outpatient clinic</td>
<td></td>
</tr>
<tr>
<td>Bickel et al, 2011 [15]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>Erythema or discharge at the wound site with increased white count, fever, or positive cultures</td>
<td>14 d</td>
<td>Daily evaluation during the inpatient stay by surgeons blinded to allocation and up to 14 d in the outpatient clinic</td>
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<tr>
<td><strong>Mixed cases and nonabdominal surgeries</strong></td>
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<tr>
<td>Myles et al, 2007 (ENIGMA trial) [16]</td>
<td>80% vs 30% Only during surgery</td>
<td>Purulent discharge or presence of pathogens in an aseptically obtained microbial culture</td>
<td>30 d</td>
<td>Review of medical records by an investigator blinded to allocation</td>
<td></td>
</tr>
<tr>
<td>Thibon et al, 2012 [17]</td>
<td>80% vs 30% Only during surgery</td>
<td>CDC criteria</td>
<td>30 d</td>
<td>Review of inpatient medical records by an investigator blinded to allocation and a follow-up outpatient evaluation</td>
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<tr>
<td><strong>Cesarean deliveries (oxygen supplemented via face mask)</strong></td>
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<td></td>
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<tr>
<td>Gardella et al, 2008 [18]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>Administration of intravenous antibiotics for postpartum endometritis or wound infection during the initial hospital stay</td>
<td>14 d</td>
<td>House staff ascertained outcome during inpatient stay. Review of outpatient medical records.</td>
<td></td>
</tr>
<tr>
<td>Williams et al, 2013 [19]</td>
<td>80% vs 30% Surgery plus 2 postoperative hours</td>
<td>CDC criteria</td>
<td>Up to 6 wk</td>
<td>Blinded members of the treating team</td>
<td></td>
</tr>
<tr>
<td>Duggal et al, 2013 [20]</td>
<td>80% vs 30% Surgery plus 1 postoperative hour</td>
<td>Composite outcome of either surgical infection (CDC definition) or endometritis</td>
<td>Up to 6 wk</td>
<td>Daily exams in inpatient setting. Outpatient visit at 2 wk. Type of evaluator for physical examinations was not specified.</td>
<td></td>
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</tbody>
</table>

Abbreviation: CDC, Centers for Disease Control and Prevention.

* 30% oxygen was mixed with 70% nitrous oxide and 80% oxygen was mixed with 20% nitrogen.
high vs low oxygen supplementation are limited given the comparator used. Furthermore, the impact of perioperative nitrous oxide supplementation is still being hotly debated in the anesthesia literature [26–28].

In 2012, Thibon and collaborators published a study using a rather heterogeneous group of surgeries. To be included, patients had to require either an abdominal, gynecological, or breast-related surgical procedure performed under general anesthesia [17]. The authors compared the use of 80% vs 30% FiO2 only during the surgical procedure. Fifteen SSIs were diagnosed among the 226 patients who underwent the intervention (6.6%) and 15 infections among the 208 controls (7.2%; P = .81). Therefore, in this predominantly noncolorectal surgery trial, no statistically significant difference was found regarding the incidence of SSIs. It is important to highlight that this patient population is a markedly different case mix than the ones used in previous studies. Furthermore, the study was powered to detect an effect size of 50% from a baseline of 12% infection rate in the control group and thus might have been insufficiently powered.

Cesarean Deliveries

In 2008, Gardella and colleagues evaluated the impact on surgical infections of 80% oxygen supplementation among patients undergoing nonemergent cesarean deliveries, under regional anesthesia, after the onset of labor [18]. Patients were randomized to receive either 80% or 30% FiO2 during surgery and 2 hours postoperatively. Although not statistically significant, this study showed a higher rate of SSIs among patients assigned to the high oxygen group than among the controls (17/69 [25%] vs 10/74 [14%], respectively; P = .13). Two additional RCTs among cesarean sections were published in 2013. Duggal and collaborators randomized 831 patients undergoing cesarean sections to receive either 80% or 30% FiO2 during their surgical procedures and the subsequent postoperative hour [20]. Wound infections were evaluated up to 6 weeks following the procedures. The incidence of SSIs was 5.5% and 5.8% (P = .98) among the high and low oxygen supplementation groups, respectively. In a similar population, Williams et al found SSI rates of 13% (10/77) in the 80% FiO2 group and 14.5% (12/83) in the 30% FiO2 group (P = .82) [19]. Therefore, studies performed among women undergoing cesarean deliveries [18–20, 29] utilizing high oxygen supplementation through face masks during surgery failed to show an impact on SSIs against controls (30% FiO2). These results might not only be associated with the type of procedure (eg, cesarean delivery instead of colorectal surgery), but also due to the method of oxygen delivery. Both the use of a mask rather than mechanical ventilation to deliver oxygen and the potential lack of compliance with the intervention during the postoperative period might have influenced the degree of tissue oxygenation attained, subsequently affecting the rate of SSIs [29].

Table 2. Published Randomized Controlled Trials: Number of Patients by Group Allocation, Type of Surgery, and Surgical Site Infection Rates

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Participants (High vs Low Oxygen Groups)</th>
<th>Type of Surgery</th>
<th>Surgical Site Infection Rates (High vs Low Oxygen Groups)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grief et al, 2000 [10]</td>
<td>250 vs 250</td>
<td>Elective colorectal surgeries</td>
<td>5.2% vs 11.2%</td>
<td>.01</td>
</tr>
<tr>
<td>Pryor et al, 2004 [11]</td>
<td>80 vs 80</td>
<td>Major abdominal procedures (including colorectal cases and large gynecologic debulking procedures involving bowel)</td>
<td>25% vs 11.3%</td>
<td>.02</td>
</tr>
<tr>
<td>Belda et al, 2005 [12]</td>
<td>148 vs 143</td>
<td>Elective colorectal surgeries</td>
<td>14.9% vs 24%</td>
<td>.04</td>
</tr>
<tr>
<td>Mayzler et al, 2005 [13]</td>
<td>19 vs 19</td>
<td>Elective colorectal surgeries for malignancies</td>
<td>12.5% vs 17.6%</td>
<td>.53</td>
</tr>
<tr>
<td>Meyhoff et al, 2009 (PROXI trial) [14]</td>
<td>685 vs 701</td>
<td>Acute or elective laparotomies</td>
<td>19.1% vs 20%</td>
<td>.51</td>
</tr>
<tr>
<td>Bickel et al, 2011 [15]</td>
<td>107 vs 103</td>
<td>Appendectomies</td>
<td>5.6% vs 13.6%</td>
<td>.04</td>
</tr>
<tr>
<td>Myles et al, 2007 (ENIGMA trial) [16]</td>
<td>997 vs 1015</td>
<td>General anesthesia cases</td>
<td>7.7% vs 10%</td>
<td>.036</td>
</tr>
<tr>
<td>Thibon et al, 2012 [17]</td>
<td>226 vs 208</td>
<td>Mixed cases (abdominal, gynecological, and breast surgeries)</td>
<td>6.6% vs 7.2%</td>
<td>.81</td>
</tr>
<tr>
<td>Gardella et al, 2008 [18]</td>
<td>69 vs 74</td>
<td>Elective cesarean deliveries under regional anesthesia after onset of labor</td>
<td>25% vs 14%</td>
<td>.13</td>
</tr>
<tr>
<td>Williams et al, 2013 [19]</td>
<td>77 vs 83</td>
<td>Cesarean deliveries</td>
<td>13% vs 14.5%</td>
<td>.82</td>
</tr>
<tr>
<td>Duggal et al, 2013 [20]</td>
<td>416 vs 415</td>
<td>Elective or emergency cesarean deliveries</td>
<td>5.8% vs 5.5%</td>
<td>.98</td>
</tr>
</tbody>
</table>
THIRD VARIABLES

The heterogeneity of the above RCTs constitute one of the main challenges on their interpretation. These studies are not only different in regard to their interventions, outcomes, patient population, and surgical procedures, but also on the degree of standardization of third variables. As Hunt and Hopf nicely pointed out, wound oxygen levels increase during oxygen supplementation only in the absence of vasoconstriction [23]. Therefore, covariates that might be playing a role in the association of oxygen supplementation and subsequent SSIs include degree of blood loss, aggressiveness of fluid resuscitation, type of fluid used for volume replacement, bowel preparation, and rigorous temperature control. For example, in some of the studies favoring high oxygen supplementation, such as Grief et al, Belda et al, and Bickel et al [10, 12, 15], aggressive hydration or normothermia were part of the study protocols; however, this standardization of third variables might have not been so rigorously done by other studies [11, 14]. A couple of tables summarizing some of these covariates can be found in a recently published meta-analysis [30]. Additionally, gases used for mixing oxygen fractions constitute another potential variable playing a role in this association.

NONINFECTIOUS SIDE EFFECTS

One of the main concerns of 100% oxygen supplementation is the potential development of adverse events. Previous studies have described the development of lung damage that ranges from mild local disease to a more diffuse alveolar involvement such as acute respiratory distress syndrome [31–33]. However, other experiences supplementing high oxygen fractions lower than 100%—such as 80% oxygen—did not seem to be associated with these pulmonary complications [34].

The PROXI trial found a rate of atelectasis among the high oxygen group of 7.9% (54/685) compared to 7.1% among the control group (50/701; \( P = .56 \)) [14]. The rates of respiratory failure and pneumonia were also not statistically different between the 2 groups. Similarly, Thibon and colleagues reported a lack of statistically significant difference in regard to nausea or vomiting, sternal pain, or hypotension between the 2 oxygen supplementation groups [17]. The ENIGMA trial found that the nitrous oxide–free group (80% oxygen supplementation) had less incidence of postoperative nausea and vomiting, fever, pneumonia, or atelectasis than the nitrous oxide–based group (30% oxygen) [16]. However, these differences might be related to the presence or absence of nitrous oxide rather than the actual oxygen concentrations.

One of the meta-analyses described below nicely summarized the pulmonary outcomes (ie, atelectasis, blood gases, lung spirometry, and postoperative oxygen saturation) of 9 RCTs that used high oxygen supplementation (80%–100% \( \text{FiO}_2 \)) against controls (30%–40% \( \text{FiO}_2 \)) [30]. Atelectasis was reported by 4 of the studies, with incidence rates of 8.3% and 10.6% in the high and low oxygen groups, respectively (relative risk = 0.93; 95% confidence interval: 0.59–1.46). Nevertheless, a trial performed among 142 moderately obese patients showed better spirometry values both during surgery and postoperatively among the lower oxygen supplementation group [35].

META-ANALYSES

There have been almost as many meta-analyses on the effect of oxygen supplementation on wound infections as RCTs. Of course, these meta-analyses were performed in different years and thus the studies used to base their conclusions differed among them (Table 3). Additionally, doing a meta-analysis is complicated by the fact that many of the RCTs described above are rather heterogeneous in regard to the gas mixture/actual \( \text{FiO}_2 \), type of patients studied, the definition of the outcome, time of follow-up, etc. As of early 2013, there were 8 meta-analyses available. Six meta-analyses concluded that there was moderate to high probability of decreasing SSIs by using high inspired oxygen: 3 found a statistically significant benefit only among colorectal procedures [36, 38, 41], 1 found positive results in subgroups consisting of either colorectal surgeries or procedures requiring general anesthesia (rather than neuroaxial anesthesia) [40], and 2 found benefit in all types of surgeries evaluated [30, 37] (Table 3).

Only 2 of the 8 meta-analyses concluded that high inspired oxygen was not associated with lower incidence of SSIs [29, 39]. One of them was performed using cesarean procedures with oxygen supplemented through face masks (see comments above) [29]. The second also failed to show differences in the incidence of infections; however, it determined that 30-day mortality was lower among the intervention group, which was indeed an interesting finding that is rarely discussed [39].

MORTALITY

Only 2 of the 9 RCTs had mortality as part of their specific aims. The PROXI trial evaluated 30-day mortality, finding rates of 4.4% and 2.9% in the groups that received high vs low oxygen supplementation, respectively \( (P = .13) \) [14]. The ENIGMA trial also evaluated 30-day mortality, with rates of 0.3% and 0.9% in the nitrous oxide–free (80% oxygen) and the nitrous oxide–based (30% oxygen) groups, respectively \( (P = .1) \) [16].

The investigators of both the ENIGMA and PROXI trials, the largest RCTs on use of high perioperative \( \text{FiO}_2 \), performed follow-up evaluations of their original study subjects to look at long-term mortality [42, 43].
## Table 3. Published Meta-analyses

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</thead>
<tbody>
<tr>
<td>Chura et al, 2007 [36]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.68 (0.49–0.94)</td>
<td>.02</td>
<td>High inspired oxygen was associated with lower rates of SSIs among colorectal surgeries</td>
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<tr>
<td>Qadan et al, 2009 [37]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.742 (0.599–0.919)</td>
<td>.006</td>
<td>High inspired oxygen was associated with lower rates of SSIs among all surgeries, but specially among colorectal procedures</td>
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<tr>
<td>Al-Niaimi et al, 2009 [38]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.70 (0.52–0.94)</td>
<td>.01</td>
<td>High inspired oxygen was associated with lower rates of SSIs among colorectal surgeries</td>
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<tr>
<td>Brar et al, 2009 [39]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.66 (0.47–0.92)</td>
<td>.01</td>
<td>High inspired oxygen was not associated with lower rates of SSIs (based on random effects model); however, there was improved 30-day mortality</td>
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<tr>
<td>Togioka et al, 2009 [40]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.85 (0.52–1.38)</td>
<td>.51</td>
<td>High inspired oxygen was associated with lower rates of SSIs only among colorectal and general anesthesia surgeries</td>
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<td>Kao et al, 2012 [41]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.84 (0.73–0.97)</td>
<td>.02</td>
<td>Moderate probability of benefit in regards to SSIs among colorectal surgeries</td>
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<tr>
<td>Hovaguimian et al, 2013 [30]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.77 (0.59–1.00)</td>
<td>NA</td>
<td>High inspired oxygen was associated with a lower probability of SSIs, especially among colorectal surgeries (no heterogeneity in the latter population). The intervention group did not experience increased incidence of pulmonary complications.</td>
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<tr>
<td>Klingel et al, 2013d [29]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1.12 (0.86–1.46)</td>
<td>.40</td>
<td>High inspired oxygen failed to decrease the incidence of SSIs among cesarean procedures.</td>
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</table>

Abbreviations: CI, confidence interval; NA, not available; SSI, surgical site infections.

* Table shows fixed effect model. The random effect model was not significant.

* Effect was larger when only the colorectal studies were included.

* Heterogeneity was found among the studies.

* This meta-analysis included 2 unpublished papers not referenced in this manuscript.
The patients enrolled in the PROXI trial underwent their index surgical procedures from October 2006 through October 2008, and survival determinations were performed in February 2010 (range of follow-up, 17–41 months) [43]. A total of 159 fatalities (23.2%) were described among the 685 patients who received 80% FiO2 and 128 fatalities (18.3%) were identified among 701 controls (P = .03). The authors performed a subgroup analysis looking at the effects of oxygen supplementation on mortality based on the presence or absence of cancer-related surgery. Among patients who underwent cancer surgery, 33.5% patients died who received an FiO2 of 80% compared to 24.6% patients in the 30% FiO2 group (P = .009). This difference was not observed among the noncancer surgeries.

The ENIGMA trial enrolled patients from April 2003 to November 2004 and the survival follow-up occurred during the years of 2007 and 2008, with a median follow-up of 3.5 years [42]. Three hundred eighty patients died after their index surgical procedures, 12 (3%) within the 30-day period and the remaining 368 (97%) afterward. Mortality among patients receiving nitrous oxide–based anesthesia (30% oxygen) was no different than among the nitrous oxide–free anesthesia group (80% oxygen) (hazard ratio = 0.98; 95% confidence interval, 0.8–1.2; P = .82).

CONCLUSIONS

The studies published to date on high oxygen supplementation are heterogeneous in regard to many variables, including duration of oxygen supplementation, type of gases used to mix the oxygen (ie, nitrous oxide, nitrogen, air), type of surgical procedures included, modality to determine the outcomes (ie, physical exam by study investigators, medical records review), and duration of follow-up [44]. Additionally, important covariates such as fluid resuscitation and normothermia were not equally standardized in all the subjects that participated in the RCTs. Nevertheless, oxygen supplementation during the perioperative period would seem to decrease the incidence of SSIs, with beneficial effects seen most consistently among patients undergoing colorectal surgeries. The suggestion that high perioperative FiO2 may negatively impact long-term mortality merits further study. Particular attention should be given to whether the presence of underlying malignancy could be acting on long-term outcomes as an additional variable to type of surgery and FiO2. Confirmation of that effect would have immediate impact on our conclusions that an 80% FiO2 should be considered as a likely effective intervention to decrease the incidence of colorectal SSIs.

Although logistically challenging, ideal future studies would need to be powered to determine the individual patient characteristics and types of surgical procedures that would most likely benefit from high oxygen supplementation, and to evaluate oxygen’s side effects including short-term mortality. Given the potential of a long-term negative impact, we suggest employing high FiO2 among surgical procedures (especially colorectal) requiring general anesthesia and with high rates of SSIs, not without first ensuring that other known associated factors are already being addressed, such as perioperative normothermia, normoglycemia, adequate volume replacement, and proper and timely preoperative antibiotics.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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