Effect of Perioperative Oxygen Supplementation on 30-day Surgical Site Infection Rate in Abdominal, Gynecologic, and Breast Surgery

The ISO_2 Randomized Controlled Trial

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ABSTRACT

Background: Benefits and limitations of supplementation with 80% fraction of inspired oxygen for preventing surgical site infections have not yet been clearly defined. Some studies have reported benefits in colorectal surgery, whereas trials in abdominal and gynecologic surgery have reported either no effect or a deleterious effect.

Methods: Controlled, randomized, assessor-blind multicenter trial, the ISO_2 study, comparing the effects of hyperoxygenation (fraction of inspired oxygen, 80%) with those of 30% oxygen on the frequency of surgical site infections in routine abdominal, gynecologic, and breast surgery on 434 patients. Patients not seen in consultation after discharge were contacted.

Results: In total, 208 patients received 30% perioperative oxygen and 226 received 80%. There was no difference between the two groups for baseline, intraoperative, and postoperative characteristics, except for oxygen saturation at closure, higher in the 80% group ($P = 0.01$). The frequency of 30-day surgical site infections was 7.2% (15/208) in the 30% group and 6.6% (15/226) in the 80% group (relative risk, 0.92; 95% CI [0.46–1.84], $P = 0.81$). Frequency of adverse events (nausea and vomiting, sternal pain, cough, hypotension) was similar in the two groups. Desaturation and bradycardia were more frequent in the 30% group. In an updated meta-analysis including the result of this trial and those of eight published randomized trials, the overall relative risk was 0.97; 95% CI (0.68–1.40), I^2 (inconsistency degree) = 73%, ($P = 0.88$).

Conclusions: The routine use of hyperoxygenation throughout abdominal, gynecologic, and breast surgery had no effect on the frequency of 30-day surgical site infections and was not accompanied by more frequent adverse effects.

What We Already Know about This Topic

- There are conflicting results regarding the effect of high quantities of oxygen utilized perioperatively on preventing surgical site infections

What This Article Tells Us That Is New

- Routine delivery of 80% FiO_2 in abdominal, gynecologic, and breast surgery did not decrease the incidence of 30-day surgical site infections

SURGICAL-SITE infections (SSI) are frequent, potentially serious, and costly.[1–3] The fight against such infections is a daily concern of surgical, anesthesiology, and infection control teams. The risk factors for SSI are related to the characteristics of the patients, the surgical procedures carried out, and perioperative conditions. Scientific societies have issued recommendations[4] for reducing the risk of SSI. In addition to major preoperative prevention measures (antibiotic prophylaxis and preparation of the skin of the patient undergoing surgery), these recommendations include impor-

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tant peri- and postoperative measures: management of body temperature,[5] volemia,[6] glycemia[7] and postoperative pain.[8]

Hyperoxygenation is another theoretical preventive measure. Through the production of superoxide radicals, oxygen plays a key role in the bactericidal activity of neutrophils[9,10] and, thus, in defense against infection. An increase in the partial pressure of oxygen in the tissues increases the production of superoxide radicals,[11] and the levels of these radicals are correlated with the frequency of SSI.[12]

Several trials have assessed the effect of hyperoxygenation using 80% fraction of inspired oxygen (FiO_2) on the occurrence of SSI,[13–20] and have generated conflicting results. Trials in colorectal surgery have shown a beneficial effect of hyperoxygenation, with a halving of the frequency of SSI, whereas trials in other types of surgery have revealed an absence of effect, or even a deleterious effect.

After the publication of the first studies, many anesthesiologists asked themselves whether hyperoxygenation might be beneficial for routine surgery. The procedure is simple, cheap, and easy to implement. However, many questions remain unanswered concerning the adverse effects that might be induced by hyperoxia, particularly those of a respiratory nature. In addition, changing practices based on a single randomized trial may not be justified.

The aim of this study was to evaluate the effects of hyperoxygenation to 80% FiO_2 in routine abdominal and gynecologic surgery on the frequency of SSI occurring during the 30 days following surgery, and to compare the frequencies of peri- and immediate postoperative adverse effects between a group of hyperoxygenated patients and a group of patients receiving 30% oxygen.

Materials and Methods

We carried out a multicenter, assessor-blind, randomized, controlled, parallel-group study in the Basse-Normandie region of France. We enrolled 434 patients between June 1, 2003, and June 30, 2007.

Patients were recruited by staff anesthesiologist investigators during the preanesthetic consultation. Subjects were considered eligible if they were at least 18 yr old and were scheduled to undergo elective abdominal, gynecologic, and breast surgery. We aimed to study routine surgery, so all interventions falling into these three categories were included, provided that general anesthesia was required. The exclusion criteria were a recent history of fever and/or infection, chronic respiratory failure (oxygen Pa_{O_2} below 60 mmHg, 8.9 kPa at rest), and bleomycin treatment (which may induce sensitivity to oxygen toxicity).

The French Medicines Agency and the regional ethics committee (Centre de Protection des Personnes, Caen, France) approved the trial, and written informed consent was obtained from all patients. This study was registered in the French Health Products Safety Agency (AFSSAPS), identifier 021178, in compliance with the French policy at the time the trial started.

Study Protocol

Before the induction of anesthesia, each patient was preoxygenated (100% FiO_2) *via* a facemask for at least 3 min until the tele-expiratory fraction of oxygen was at least 90%. After intubation, the patient was ventilated with an anesthesia respirator, and anesthesia maintenance was left to the discretion of the anesthetist in charge of the patient. After the induction of anesthesia and tracheal intubation, patients were assigned to one of two groups (30% or 80% FiO_2) according to a computer-generated allocation list without blocking or stratification. The anesthesiologist caring for the patient had a restricted access to this computer, close to the operating theater. Only the anesthesiologists were aware of the group to which the patients had been allocated. The intraoperative administration of gas at the indicated concentration continued until extubation. During extubation, the proportion of oxygen was increased to 100%. In cases in which extubation was delayed beyond the end of the intervention, the FiO_2 was maintained at the programmed level by the respirator. During the postoperative period, oxygen was administrated at the physician's discretion.

Evaluation

For each patient, we recorded age, sex, weight, height, body mass index, American Society of Anesthesiologists physical class status, current smoking, and history of cancer or diabetes mellitus. Biologic data included preoperative hemoglobin concentration and white cell count. Peripheral arterial oxygen saturation was measured with a pulse oxymeter and recorded at the induction of anesthesia. At closure, oxygen saturation, hemoglobin concentration (measured noninvasively), and core temperature (measured in the distal esophagus) were recorded. Surgical procedures data included the type of surgery, surgery duration, wound class (clean, clean-contaminated, contaminated, or dirty-infected), type of anesthesia (inhalational or totally intravenous), use of prophylactic intravenous antibiotics, and need for transfusion (with the number of units transfused, as appropriate). We also recorded instances in which it was not possible to maintain the study protocol for the entire duration of the intervention, and the reasons for this. We used the National Nosocomial Infection System risk index[21] to evaluate the risk of infection. This score ranges from 0 (low risk) to 3 (highest risk), and takes into account wound class, American Society of Anesthesiologists status, and duration of surgery. After surgery, the destination of the patient was noted (postanesthesia care unit or intensive care unit), together with postoperative oxygen use (with dose and duration). When the patient left the postanesthesia care unit, the following clinical data were recorded: presence of nausea or vomiting, cough, sternal pain, visual, or auditory disorder.

We used the definitions of the Centers for Disease Control and Prevention[22,23] for the diagnosis of SSI. According to these definitions, all SSI occurring within 30 days of surgery were included and classified as superficial, deep wound,

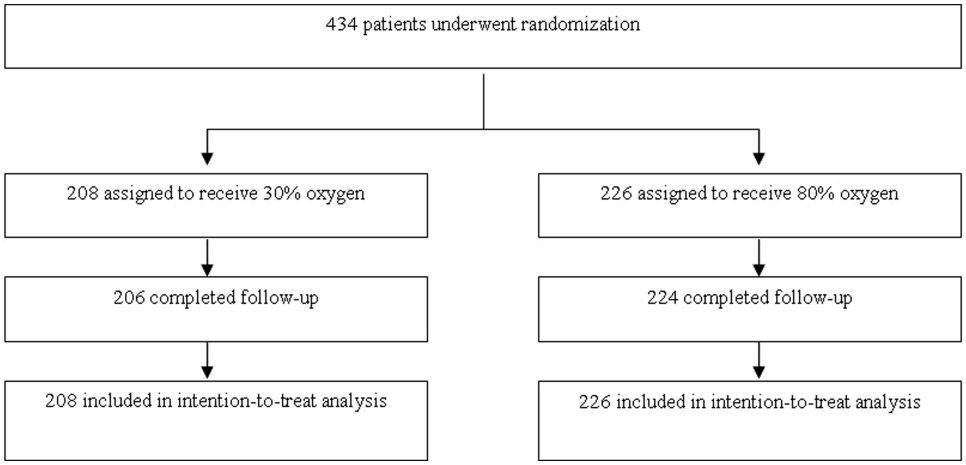

Fig. 1. Trial recruitment and flow. The patients who withdrew were assumed to be uninfected.

or organ/space infection. We checked for evidence of SSI by having an investigator blind to the randomization conduct a systematic review of each patient's medical records, including the documentation provided by physicians and nurses and laboratory reports. After discharge from hospital, patients were seen for a follow-up visit within 30 days. This visit included an assessment of the patient's infection status. If patients did not attend the postoperative visit, the investigator assessed their infection status by calling their physician, or directly calling the patient.

Statistical Analysis

The baseline postoperative infection rate in the control group was estimated *pro rata* from the rates reported in previous studies and in published reports of wound infection surveillance.[24]

Based on an infection rate of 12% in the control group, a δ value of 50%, $\alpha = 5\%$ (two-tailed), $\beta = 20\%$ (statistical power = 80%), we estimated that n = 270 patients per treatment group were required for this study.

The analysis was carried out on an intention-to-treat basis. Patients remained within the group to which they were assigned, even if the concentration of oxygen was increased during the intervention to maintain adequate saturation.

The primary outcome (percentage of patients with 30-day SSIs in each group) was analyzed with two-tailed chi-square tests. Relative risk (RR) of SSI and corresponding 95% CI were computed. Other outcomes were analyzed with the chi-square test, Fisher exact test, Student *t* test or Mann–Whitney U tests, as appropriate. In addition, a temporal trend in SSI was tested by Cochran–Armitage test.

In order to contrast and interpret our research in the context of prior studies relevant to our study, we conducted a systematic review and meta-analysis of the effect of supplemental oxygen therapy on surgical site infection rate. We searched Medline for full-text articles published from January 1999 to December 2011, in English or French, reporting randomized controlled trials or meta-analyses of randomized controlled trials. We used the terms "surgical site infection," "random*," and "oxygen*." We also searched the reference lists of retrieved articles. We identified two meta-analyses, both published in 2009.[25,26] Three additional randomized trials [18–20] together with our trial were conducted after the two meta-analyses were published. One trial[27] was excluded because the intervention was not supplemental oxygen. Updated cumulative RR of surgical site infection and their 95% CI were computed for each qualified study. Heterogeneity was assessed by chi-squared test and the I^2 statistics. I^2 indicates the percentage between study variability which is not explained by chance variability. Study-specific RRs were pooled using a random-effect model with the Mantel–Haenszel weighting method.

A two-tailed $P < 0.05$ was considered statistically significant. Analyses were performed using SAS (version 9.2, SAS, Cary, NC) and Review Manager (RevMan Version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Demark).

Results

During the study, we enrolled and randomized 434 patients: 225 (52%) at the François Baclesse Cancer Institute (Caen, France, center No. 1), 168 (39%) at Caen University Hospital (Caen, France, center No. 2), 31 (7%) at the Saint Martin Private Hospital (Caen, France, center No. 3), and 10 (2%) at Coutances Hospital (Coutances, France, center No. 4). For 72.1% of patients, infection status was assessed during a follow-up visit, and for 117 patients (27.0%), post-discharge assessment was performed. Four patients were lost to follow-up. They had no known infection when they left the hospital and were therefore considered to be uninfected in our analysis (fig. 1).

These 434 patients were randomized such that 208 received 30% perioperative oxygen and 226 received 80% oxygen. The characteristics of the patients enrolled in the two groups are summarized in table 1. The two groups displayed

Table 1. Characteristics of the Patients in the Two Groups

Characteristics	30% FiO_2 (N = 208)	80% FiO_2 (N = 226)
Baseline		
Age (years)	51.8 (13.3)	52.1 (13.7)
Sex (female)	184 (88.5)	208 (92.0)
Weight (kg)	66.6 (14.0)	66.2 (13.4)
Height (cm)	163 (8)	164 (7)
Body mass index (kg/cm^2)	25.0 (5.1)	24.7 (4.9)
Body mass index >30	27 (13.0)	29 (12.8)
Current smoker	42 (20.2)	39 (17.3)
Diabetes	12 (5.8)	7 (3.1)
American Society of Anesthesiologists physical status class		
ASA 1 (healthy)	106 (51.0)	113 (50.0)
ASA 2 (minimal illness)	90 (43.3)	108 (47.8)
ASA 3 (moderately ill)	12 (5.8)	5 (2.2)
Center		
No. 1	106 (51.0)	119 (52.7)
No. 2	80 (38.5)	88 (38.9)
No. 3	16 (7.7)	15 (6.6)
No. 4	6 (2.9)	4 (1.8)
Operative site		
Gastric/hernia	16 (7.7)	13 (5.8)
Hepatobiliary	11 (5.3)	7 (3.1)
Colon/rectum	11 (5.3)	19 (8.4)
Small bowel	5 (2.4)	4 (1.8)
Gynecologic	66 (31.8)	73 (32.3)
Breast	99 (47.6)	110 (48.7)
Cancer	108 (51.9)	120 (53.1)
Laboratory values		
Hemoglobin (g/dl)	13.4 (1.2)	13.4 (1.1)
Leucocytes (cells/μl)	6,677 (2036)	6,405 (1,728)
Intraoperative		
Prophylactic antibiotics	109 (52.4)	115 (50.9)
Anesthesia technique		
Intravenous	16 (7.7)	13 (5.8)
Inhalation	73 (35.1)	76 (33.6)
Both	119 (57.2)	137 (60.6)
Coelioscopic surgery	56 (26.9)	64 (28.3)
Red-cell transfusion	5 (2.4)	4 (1.8)
Duration of surgery (min)	84 (58)	89 (61)
Core temperature (°C)	35.7 (0.7)	35.6 (0.8)*
Oxygen saturation on pulse oximetry at incision (mmHg)	98.6 (1.3)	98.6 (1.5)
Oxygen saturation on pulse oximetry at closure (mmHg)	98.6 (1.3)	98.9 (1.1)†
Postoperative		
Hemoglobin (g/dl)	12.3 (1.3)	12.2 (1.4)‡
NNIS score		
0	154 (74.0)	168 (74.3)
1	49 (23.6)	53 (23.5)
2	5 (2.4)	5 (2.2)

Data are mean (SD) or number (%). Percentages may not total to 100 because of rounding.

* Six missing values in the 30% FiO_2 group, and four in the 80% FiO_2 group. † $P < 0.05$. ‡ Ten missing values in the 30% FiO_2 group, and nine in the 80% FiO_2 group.

ASA = American Society of Anesthesiologists status; FiO_2 = fraction of inspired oxygen; NNIS = National Nosocomial Infection Surveillance System, ranging from 0 to 3 and indicating the number of risk factors present (including patient with an ASA preoperative status of 3 or higher, an operation classified as contaminated or dirty-infected, and an operation with a duration exceeding a defined threshold, depending on the operative procedure performed).

no significant differences in baseline characteristics (including age, sex, body mass index, current smoking, diabetes or cancer, American Society of Anesthesiologists status, study center, operative site and preoperative laboratory values). A comparison of the intraoperative and postoperative characteristics of the two groups identified a difference only in oxygen saturation on pulse oximetry at closure, which was higher in the 80% FiO_2 group ($P = 0.01$).

The protocol was not maintained for the entire duration of the operation in 13 cases (6.3%) from the 30% group and three cases (1.3%) from the 80% group ($P = 0.007$). The reasons for deviation from the protocol were desaturation

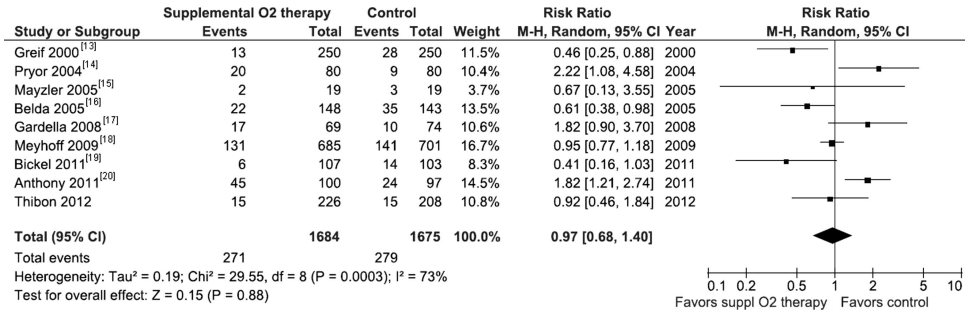

Fig. 2. Results of the updated meta-analysis, including information from previous studies and relative risk ratios.

and/or bradycardia in the 30% group, and intraoperative complications, including one case of septic shock, in the 80% group.

The global frequency of SSI was 6.9% (30/434). The frequency of SSI was 7.2% (15/208) in the 30% FiO_2 group and 6.6% (15/226) in the 80% FiO_2 group ($P = 0.81$), with a RR of 0.92 (95% CI [0.46–1.84], $P = 0.81$). No significant temporal trend was found for the primary outcome, neither in the 30% group ($P = 0.84$), nor in the 80% group ($P = 0.91$).

The most common postoperative adverse events were nausea and vomiting, which occurred in 17 of the 226 patients in the 80% oxygen group (7.5%) and 11 of the 208 patients in the 30% oxygen group (5.3%; $P = 0.34$). Sternal pain occurred in five patients in the 80% oxygen group (2.2%) and six (2.9%) patients in the 30% group (2.9%, $P = 0.66$). The other postoperative adverse events observed were cough (one case in the 80% group), hypotension (three cases in the 80% group *vs.* zero in the 30% group, $P = 0.10$). No visual or auditory disorder was noted.

We observed six superficial, four deep, and five organ/space infections in the 30% FiO_2 group, and six superficial, five deep, and four organ/space infections in the 80% group ($P = 1.00$). The mean time between surgery and SSI diagnosis was 15.4 days ± 8.2 overall (16.9 days ± 8.0 in the 80% group *vs.* 13.9 days ± 8.4 in the 30% group).

Cultures of pus were obtained for 22 of 30 patients, with a positive result obtained in 18 cases. The causal microorganisms identified were *Staphylococcus aureus* (eight cases), coagulase-negative staphylococcal species (four cases), *Pseudomonas aeruginosa* (two cases), and Gram-negative bacteria (four cases).

The nine trials included in the meta-analysis enrolled 3,359 patients. We detected significant heterogeneity between studies (I2 = 73%, chi-square = 29.55, $P < 0.0003$). The overall RR was 0.97; 95% CI (0.68–1.40), $P = 0.88$, as shown in figure 2.

Discussion

We found no evidence that the perioperative administration of 80% FiO_2 during routine abdominal, gynecologic, and breast surgery could decrease the frequency of SSI in the first 30 days after surgery. Hyperoxygenation (80% FiO_2) was not accompanied by an increase in secondary effects, such as dry cough, retrosternal pain, or vision problems. Desaturation and/or bradycardia occurred more frequently in the 30% group as compared with the 80% FiO_2 group ($P = 0.007$).

With the aim of maximizing the external validity of our results, we decided to carry out this study in the context of current practice, respecting the routine practices of the surgical teams involved. We therefore included nonuniversity and private-sector centers in this study. Another particularity is that important efforts were made to ensure exhaustive follow-up, particularly after discharge from hospital. Several studies have shown that SSI occurring after discharge from hospital[28–31] may account for up to 70% of all SSI. We strengthened the follow-up of patients who did not return for follow-up visits by collecting the necessary information from their doctors or from the patients themselves.

One of the limitations of this study is its sample size, which was smaller than planned, decreasing the statistical power of the study. Enrollment difficulties were encountered, mostly because the problem of nosocomial infections (including SSI in particular) was highly publicized in France at the time of the study. The study was therefore prematurely ended because of elapsed time. The various measures taken to overcome this problem (changes to the information letter provided to patients, considerable lengthening of the duration of the study) made it possible to secure 94% of the planned number of subjects. Another limitation of this study was the frequency of SSI in the control group (7.2%), which was much lower than predicted for this type of surgery (14%). For this initial estimation of SSI rates, we took into account a high proportion of SSI cases occurring after hospitalization and the fact that our definition of SSI covered a period of up to 30 days after surgery.[22,23] To address these potential limitations, we conducted a meta-analysis (fig. 2) including our results. The findings of the meta-analysis (RR: 0.97; 95% CI [0.68–1.40]) are consistent with our results (RR: 0.92, 95% CI [0.46–1.84]), suggesting no effect of 80% FiO_2 in SSI reduction.

One of the unique features of our study was the use of hyperoxygenation only during the intervention and not continuing into the immediate postoperative period. Previously published trials retained the patients in their oxygenation groups, with the maintenance of oxygenation conditions for

the first 2 h of the postoperative period[13,14,16–19] or for 6 h.[15] In our study, this would have required the use of nonrebreather masks in the recovery room, which is not routine practice in France and would therefore not have been compatible with our objectives.

Our results confirmed those obtained by Meyhoff in the PROXI study.[18] The PROXI study included almost 1,400 patients and concerned types of surgery similar to those studied here. The odds ratio between the two groups was 0.94 (0.72–1.22), $P = 0.64$. Two other studies reported no effect of hyperoxygenation on the risk of SSI.[16,17] The single-center study carried out by Mayzler[16] on surgery for colorectal cancer had a small statistical power (only 38 patients included). The study by Gardella[17] concerned cesarean section and was stopped for reasons of futility after the inclusion of 143 patients, an interim analysis having shown a doubling of the frequency of SSI in the 80% group, indicating that continuation of the trial could not lead to the demonstration of a beneficial effect of hyperoxygenation.

Among trials reporting a superiority of peri- and postoperative oxygenation to 80%,[13,17,19] two concerned major colorectal surgery to treat cancer or a chronic inflammatory disease. Both trials excluded "minor" colorectal surgery (polypectomy, for example). The first trial, carried out by Greif,[13] reported a spectacular effect in the treated group, with a decrease in the frequency of SSI by almost 50% at 14 days (13/250 = 5.2% in the 80% group *vs.* 28/250 = 11.2% in the 30% group; $P = 0.01$). The quality of randomization appeared to be high in this study, although there was no comparison of diabetes history between the two groups. In the other study,[15] the 80% group contained significantly more women, with a mean body mass index of 27.1, *versus* 26.5 for the control group (nonsignificant). History of diabetes was again not considered.

The trial carried out by Pryor[14] and published shortly after that of Greif[13] concerned abdominal surgery and reported very different results: Hyperoxygenation was associated with a strong increase in the risk of SSI, resulting in the trial being stopped after the interim analysis. In this study, higher body mass index in the 80% group (27.1 *vs.* 25.1, $P = 0.04$) may explain in part the higher rate of SSI in this group. Diabetes and being overweight are two major risk factors for SSI.[32–35] In the PROXI study,[18] history of diabetes and body mass index (less than 30 or more than or equal to 30) were among the stratification variables used for randomization.

The reasons for the limitation of a possible effect of hyperoxygenation on the risk of infection to major colorectal surgery have not been clearly established. Trials on other types of surgery and reporting an absence of effect or a deleterious effect did not differ with trials in major colorectal surgery by either the duration of oxygen administration or by the way in which the oxygen was administered. Other possible reasons should be explored and other trials in the domain of colorectal surgery may be required.

Nausea and vomiting were the most frequent adverse effects observed, with no difference in frequency between the two groups, thus failing to confirm a previous observation that hyperoxygenation reduced the frequency of nausea and vomiting.[36] Recent guidelines do not support the use of supplemental oxygen to reduce the occurrence of postoperative nausea and vomiting.[37]

Three cases of hypotension were noted in the 80% group, with none in the 30% group (nonsignificant). We took particular care to ensure that possible secondary effects potentially linked to hyperoxia were recorded: dry cough, retrosternal pain, or vision problems. Hyperoxia may lead to surfactant changes, because of damage to proteins and certain alveolar cells.[38] Clinically, this toxicity leads to signs of tracheal or bronchial irritation, such as dyspnea, retrosternal pain, or coughing.[39] Signs of atelectasis have also been observed during hyperbaric oxygen administration or the administration of 100% oxygen for more than 24 consecutive hours.[38,40] However, studies on the frequency of postoperative atelectasis[41] or pulmonary volume on spirometry[42] after surgery have shown no deleterious effect of hyperoxygenation. In terms of toxicity to the eye, retinopathy of prematurity is linked to the exposure of the retina to high concentrations of oxygen and is a classic complication of hyperoxia linked to the immaturity of antioxidant systems in premature infants.[43] In the end, we found only one case of dry cough among the patients in the 80% oxygen group, the frequency of retrosternal pain was the same in both groups, and no vision problems were reported. The use of 80% oxygen also led to no increase in pulmonary complications in the PROXI study,[18] with similar rates of atelectasis, pneumonia, and respiratory failure in the two groups.

In conclusion, this study shows that the routine use of hyperoxygenation throughout surgical interventions in abdominal, gynecologic, and breast surgery has no major effect on the frequency of SSI. It also shows that hyperoxygenation does not increase the frequency of adverse effects. Moreover, the question as to whether hyperoxygenation has a small effect in routine surgery is not supported by the results of our updated meta-analysis, despite significant heterogeneity between studies.

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