Supplemental Perioperative Oxygen and the Risk of Surgical Wound Infection

A Randomized Controlled Trial

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Context Supplemental perioperative oxygen has been variously reported to halve or double the risk of surgical wound infection.

Objective To test the hypothesis that supplemental oxygen reduces infection risk in patients following colorectal surgery.

Design, Setting, and Patients A double-blind, randomized controlled trial of 300 patients aged 18 to 80 years who underwent elective colorectal surgery in 14 Spanish hospitals from March 1, 2003, to October 31, 2004. Wound infections were diagnosed by blinded investigators using Centers for Disease Control and Prevention criteria. Baseline patient characteristics, anesthetic treatment, and potential confounding factors were recorded.

Interventions Patients were randomly assigned to either 30% or 80% fraction of inspired oxygen (FIO_2) intraoperatively and for 6 hours after surgery. Anesthetic treatment and antibiotic administration were standardized.

Main Outcome Measures Any surgical site infection (SSI); secondary outcomes included return of bowel function and ability to tolerate solid food, ambulation, suture removal, and duration of hospitalization.

Results A total of 143 patients received 30% perioperative oxygen and 148 received 80% perioperative oxygen. Surgical site infection occurred in 35 patients (24.4%) administered 30% FIO_2 and in 22 patients (14.9%) administered 80% FIO_2 (P=.04). The risk of SSI was 39% lower in the 80% FIO_2 group (relative risk [RR], 0.61; 95% confidence interval [CI], 0.38-0.98) vs the 30% FIO_2 group. After adjustment for important covariates, the RR of infection in patients administered supplemental oxygen was 0.46 (95% CI, 0.22-0.95; P=.04). None of the secondary outcomes varied significantly between the 2 treatment groups.

Conclusions Patients receiving supplemental inspired oxygen had a significant reduction in the risk of wound infection. Supplemental oxygen appears to be an effective intervention to reduce SSI in patients undergoing colon or rectal surgery.

Trial Registration ClinicalTrials.gov Identifier: NCT00235456

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SURGICAL WOUND INFECTIONS prolong hospitalization by an average of 1 week and substantially increase the cost of care.[1,2] These infections are possibly the most common serious complication of surgery and anesthesia.[3] The primary defense against surgical pathogens is oxidative killing by neutrophils. Oxidative killing is a function of tissue oxygen partial pressure throughout the range of observed values.[4] As might be expected, infection risk depends on tissue oxygen partial pressure[5] and, therefore, interventions that increase tissue oxygen may reduce infection risk.

Greif et al[6] have shown that providing 80% oxygen throughout surgery and for 2 postoperative hours de-

See also p 2091 and Patient Page.

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creased infection risk by half compared with patients who were administered 30% oxygen (5% vs 11%). However, a recent study by Pryor et al[7] concluded that the risk of infection in a general surgical population doubled in patients who were administered supplemental oxygen during surgery (25% vs 11%). In light of this disparity, we tested the hypothesis that supplemental perioperative oxygen reduces the risk of wound infection.

METHODS

Patient Characteristics

We enrolled 300 patients aged 18 to 80 years between March 1, 2003, and October 31, 2004, who underwent elective colorectal resection in 14 hospitals in Spain. Patients having abdominal-peritoneal reconstructions were included but not those scheduled for minor colon surgery (eg, polypectomy, isolated colostomy) or laparoscopic surgery. The ethics committee at each hospital approved the protocol and written informed consent was obtained from each patient.

Exclusion criteria included expected surgery time of less than 1 hour, fever or existing signs of infection, diabetes mellitus (type 1 or 2), human immunodeficiency virus infection, weight loss exceeding 20% in the previous 3 months, serum albumin concentration of less than 30 g/L, and a leukocyte count of less than 2500 cells/mL.

Study Protocol

Mechanical bowel preparation was performed with an electrolyte solution that did not contain antibiotics or antiseptics. Antibiotic prophylaxis with metronidazole plus cefoxitin or a third-generation cephalosporin was administered 60 to 90 minutes before the surgical incision and continued postoperatively for up to 48 hours. Aminoglycosides were used as an alternative to β-lactam antibiotics in patients who reported a history of cephalosporin allergy. Anesthesia induction and treatment were standardized across all patients.

Randomization to intervention was stratified by study center. Computer-generated codes were maintained in sequentially numbered opaque envelopes. The randomization envelopes were opened in the operating department after induction of anesthesia by the anesthesiologist. Patients were assigned to an oxygen/air mixture with a fraction of inspired oxygen (FIO_2) of 30% or 80%. The displays of the anesthesia machine and gas monitors were covered with cardboard shields in both the operating department and postanesthesia care unit to keep the surgical team blinded to group assignment. Patients were not informed of their group assignments.

When the operation was finished, the inhaled anesthetic was stopped and FIO_2 was increased to 100% during extubation. During the first 6 postoperative hours, all patients were administered nonrebreathing facemasks with a reservoir (Intersurgical, Wokingham, Berkshire); oxygen was provided at the randomly designated concentration at a total flow of 16 L/min. Subsequently, patients breathed ambient air, although supplemental oxygen was provided as necessary to maintain oxygen saturation as measured by pulse oximetry (SpO_2) of at least 92%.

The attending anesthesiologist in the operating department and during the initial 6 postoperative hours was independent of the team doing the wound evaluation. At the end of 6 hours, the anesthesia and postoperative records were sealed in an envelope to maintain blinding of the surgical team and the investigators who evaluated wound status. This allowed the surgical team and the wound evaluators to remain blinded during data collection.

Perioperative normothermia was maintained with circulating-water mattresses and forced-air heaters. Fluids were administered intraoperatively at a rate of 15 mL/kg per hour; blood loss was restored with crystalloids or colloids and, when necessary, with leukocyte-filtered allogeneic red blood cell concentrate. Fluid was administered at 3 mL/kg per hour during the first 6 postoperative hours and then reduced to 2 mL/kg per hour after patients were transferred to the ward. Surgical wounds were covered with conventional gauze bandages. An antiseptic solution was applied on the surface of the surgical wound, but neither intraperitoneal antibiotics nor antiseptics were instilled.

If patients reported a postoperative pain score of more than 3 cm on a 10-cm visual analog scale (0 cm indicates no pain and 10 cm indicates worst pain imaginable), they were administered intramuscular or intravenous morphine and nonsteroidal anti-inflammatory drugs. The attending surgeon, who was unaware of the patient's oxygen treatment, controlled the use of analgesic agents. The attending surgeon also determined initiation of feeding, ambulation, and the duration of hospitalization.

Measurements

Medical history was recorded and a systematic physical examination was performed preoperatively. Patients were considered to have respiratory disease when they had a history of chronic obstructive pulmonary disease, asthma requiring routine medication, or other clinically important respiratory impairment. Laboratory testing included a complete blood cell count; biochemical analysis, including blood glucose; and coagulation tests. Infection risk was evaluated using the Study on the Efficacy of Nosocomial Infection Control (SENIC) scale.[3] The National Nosocomial Infections Surveillance System (NNISS) scale[8] was also used, which includes an evaluation of physical condition according to the American Society of Anesthesiologists physical status score.[9] The SENIC and NNISS scores have been extensively validated, and larger values with these scores indicate a greater risk of infection.

Electrocardiogram, heart rate, noninvasive blood pressure, FIO_2, SpO_2, and end-tidal concentrations of carbon dioxide and sevoflurane were continuously monitored during the surgery.

Electrocardiogram, heart rate, noninvasive blood pressure, SpO_2, and FIO_2 were monitored while the patient remained in the recovery room. An arterial blood sample was obtained 1 hour after induction of anesthesia to evaluate partial pressure of oxygen (PaO_2); another sample was obtained 2 hours after extubation. Core temperature was recorded from the tympanic membrane.

Surgical wounds were assessed daily for infection by surgeons who were unaware of patients' treatment groups. Wounds were considered infected when they met Centers for Disease Control and Prevention definitions.[10] Purulent exudates were cultured and, when positive for pathogenic bacteria, appropriate antibiotic treatment was initiated. Only those infections diagnosed during the first 14 postoperative days were included.

Wound healing characteristics were also evaluated using the ASEPSIS score (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, and duration of inpatient Stay).[11] This is an established and validated system that is derived from the weighted sum of points assigned for the following factors: duration of antibiotic administration; drainage of pus with the patient under local anesthesia; debridement of the wound with the patient under general anesthesia; serous discharge; erythema; purulent exudate; separation of deep tissues; isolation of bacteria from discharge; and hospitalization exceeding 14 days. A daily score of 20 or more was considered evidence of infection.[12]

Discharged patients were observed in the outpatient surgical clinic to assess wound status on day 15. Records were kept of physical examinations, heart rate, noninvasive blood pressure, temperature, and laboratory test results (similar to those obtained preoperatively) after 24 hours and on the day of hospital discharge; these values were also recorded on postoperative days 4, 7, 10, and 14 in patients who remained hospitalized. The times of return of bowel function, restarting feeding, ambulation, and removal of staples were also recorded. A record was also kept of whether patients had any of the following risk factors: urinary catheter, central venous catheter, mechanical ventilation, treatment with immunosuppressant medications, or parenteral nutrition.

Statistical Analysis

A preliminary study indicated that the baseline infection rate in patients undergoing major colon or rectal surgery was 25% in 3 of the participating centers. Although this incidence appears large, it is consistent with literature indicating that the infection rate in high-risk patients, such as in our study, ranges up to 36%[13] and that rates of infection are usually underestimated by clinicians.[14] Sample size analysis indicated that 300 patients would be required to provide 80% power for detecting a 50% reduction in wound infection rate at α=.05. We therefore planned to enroll 300 patients. Our primary outcome was any surgical site infection (SSI); secondary outcomes included return of bowel function and ability to tolerate solid food, ambulation, suture removal, and duration of hospitalization.

An independent data and safety monitoring board blinded to group assignment evaluated the case-report forms from each patient. Data from forms that were substantially incomplete, either because the patient dropped out of the study or because of data collection problems, were excluded from further analysis but included in a sensitivity analysis. Data from patients who were unexpectedly switched to laparoscopic procedures after enrollment were excluded from the analyses.

Intraoperative values were averaged over time in each patient; these means were then averaged across the entire treatment group. The distribution of the principal continuous variables in each group was compared using 2-tailed *t* tests for parametric data. χ^2 Tests were used for discrete variables. Mann-Whitney *U* (Wilcoxon) tests were used for nonparametric data. Data were reported as mean (SD), unless otherwise indicated; $P<.05$ was considered statistically significant. Statistical analyses were performed by using SPSS version 11.0 (SPSS Inc, Chicago, Ill).

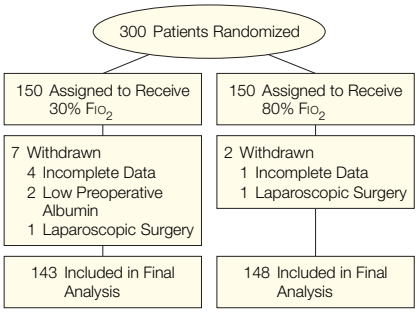
The risk of SSI associated with each study group and other potential risk factors was determined by calculating the cumulative incidence. To evaluate the relationship between the FIO_2 group and other potentially predictive factors and wound infection, the respective relative risks (RRs) were calculated. Finally, a logistic regression analysis was performed to determine the effect of 80% FIO_2 adjusted for the remaining potential risk factors for wound infection and the effect of participating hospitals. Those variables with $P<.25$ in the univariate (simple) analysis were included in the multivariate logistic regression analysis. These variables included sex, weight, age, coexisting respiratory disease, allergy, lymphocyte count, hemoglobin, glucose, and other potential wound infection predictive factors, such as SENIC and tobacco smoking.

Manipulation of variables in the model was performed using the Enter method, which forces the introduction of all the variables of interest under the specified criteria. The goodness-of-fit of the model was evaluated with the Hosmer-Lemeshow method.

RESULTS

We collected data from 300 patients who were enrolled and randomized; however, 9 patients were excluded from the main analysis because 2 had low preoperative albumin values, 2 had laparoscopic surgery (surgeon changed to laparoscopic surgery after induction of anesthesia), and 5 had incomplete case-report forms (FIGURE). Among the remaining 291 patients, 143 received 30% perioperative oxygen and 148 received 80% perioperative oxygen. Type and duration of antibiotics administered during the first 48 hours were similar in the 2 groups. The mean (SD) duration of surgery was 159 (61) minutes in patients assigned to 30% oxygen and 161 (62) minutes in those assigned to 80% oxygen (P=.80).

Figure. Trial Recruitment and Flow



FIO_2 indicates fraction of inspired oxygen.

Morphometric, demographic, and other preoperative characteristics were similar in the 2 treatment groups except that patients assigned to 80% oxygen were slightly shorter in height and more often women (TABLE 1). Other than the percentage of inspired FIO_2 and resulting PaO_2, there were no significant differences between the groups for any of the more than 30 other potential confounding factors during the operation or in the postoperative care unit. Other than postoperative hemoglobin, all physiological variables, laboratory test results data (including blood glucose concentrations), ASEPSIS index, and extrinsic infection risk factors were also similar during the postoperative period through hospital discharge.

Fifty-seven patients (39.3%) were diagnosed with SSI (of these, 50 patients had cultures positive for pathogenic bacteria): 35 patients (24.4%) had an SSI in the 30% FIO_2 group and 22 (14.9%) in the 80% FIO_2 group ($P=.04$) (TABLE 2). The risk of SSI was 39% lower in the 80% FIO_2 group (RR, 0.61; 95% confidence interval [CI], 0.38-0.98) vs the 30% FIO_2 group (TABLE 3). Among the 9 patients who were excluded from the data analysis, none appeared to have wound infections; however, follow-up was incomplete in this group and 1 patient died of sepsis. Because a true intention-to-treat analysis could not be completed secondary to incomplete follow-up data, we conducted a sensitivity analysis based on treatment group assignment that included all patients except those 4 who should have been excluded based on a priori exclusion criteria (2 had laparoscopic surgery and 2 had low preoperative albumin values). Repeating the analysis, assuming that none of the other 5 excluded patients developed an SSI, resulted in an RR reduction of 0.62 (95% CI, 0.38-1.00; $P=.05$) associated with 80% FIO_2. Repeating the analysis, assuming that these 5 excluded patients all developed infection, resulted in an RR reduction of 0.58 (95% CI, 0.37-0.92; $P=.02$).

Other outcomes did not vary significantly between treatment groups (Table 2), although fewer patients in the 80% group had ASEPSIS scores exceeding 20 on any postoperative day (25 [16.9%] vs 37 [25.9%], $P=.06$). Nine patients had to be admitted in the intensive care unit immediately after the operation because of postsurgical complications. Two patients died during the study period (including the 1 patient mentioned above), both from multiorgan failure of septic origin. Both of these patients were assigned to

Table 1. Patient Characteristics in the Study Analysis*

	30% FIO_2 (n = 143)	80% FIO_2 (n = 148)
Demographics		
Sex		
Men	91 (64)	71 (48)†
Women	52 (36)	77 (52)
Age, mean (SD), y	62.3 (12.5)	64.2 (11.8)
Weight, mean (SD), kg	72.6 (11.7)	72.3 (13.4)
Height, mean (SD), cm	165.4 (8.9)	163.2 (9.0)†
BMI, mean (SD)	26.5 (3.8)	27.1 (4.5)
BMI >30	21 (14.9)	26 (17.5)
Diagnosis		
Cancer	124 (86.7)	126 (85.8)
Inflammatory bowel disease	10 (7.0)	14 (9.4)
Other‡	9 (6.3)	7 (4.7)
Operative site		
Colon	95 (66.4)	94 (63.5)
Rectum	48 (33.6)	54 (36.5)
Physical status score§		
ASA I	26 (18.3)	15 (10.1)
ASA II	84 (58.4)	89 (60.1)
ASA III	33 (23.3)	44 (29.7)
Smoking status		
Nonsmoker	113 (78.9)	118 (79.5)
<20 cigarettes/d	20 (14.0)	15 (10.3)
≥20 cigarettes/d	10 (7.0)	15 (10.3)
History		
Alcohol intake >30 g/d	9 (6.5)	12 (8.2)
Previous surgery	23 (16.3)	21 (13.9)
Respiratory disease	16 (11.2)	25 (17.1)
Cardiovascular disease	31 (21.8)	41 (28.4)
Hepatic disease	11 (7.7)	11 (7.3)
Hematological disease	15 (10.7)	18 (12.2)
Renal disease	3 (2.1)	7 (4.8)
Neurological disease	2 (1.4)	5 (3.5)
Osteomuscular disease	19 (13.3)	22 (15.2)
Allergy	16 (11.3)	12 (8.1)
Other‖	31 (21.8)	36 (24.4)
Surgical procedure		
Total or subtotal colectomy	6 (4.2)	5 (3.4)
Hemicolectomy	46 (32.2)	43 (29.1)
Rectum resection with abdominal-perineal repair	14 (9.8)	15 (10.1)
Sigmoid anterior section	41 (28.7)	46 (31.1)
Rectal anterior resection	24 (16.8)	29 (19.6)
Other¶	12 (8.4)	10 (6.8)

(Continued)

the 30% oxygen group. Patients with infection had mean (SD) ASEPSIS scores on the first 6 postoperative days of 8.8 (0.81), whereas those without infections had mean (SD) scores of 6.0 (0.41) (P=.003). Patients with infection took longer to ambulate (mean [SD], 4.9 [3.2] vs 3.9 [2.1] days; P=.008), had their staples removed later (11.6 [3.6] vs 10.1 [3.2] days; P=.007), and had longer hospital stays (15.1 [8.2] vs 10.7 [4.8] days; P=.001).

In unadjusted analyses, men and those with coexisting respiratory disease were at increased risk of SSI (RR, 1.95; 95% CI, 1.06-3.61; and RR, 2.15; 95% CI, 1.03-4.48; respectively) (Table 3). After multivariate adjustment, only the percentage of inspired oxygen and coexisting respiratory disease were significantly associated with the risk of infection. After adjustment for all covariates, the risk of SSI was reduced 54% in patients assigned to 80% oxygen (RR, 0.46; 95% CI, 0.22-0.95; P = .04). Patients with coexisting respiratory disease had a 3.23-fold (95% CI, 1.18-8.86) greater probability of SSI. Including the effect of participating hospitals in the multivariate analysis did not change the RR of SSI for FIO_2.

COMMENT

In this randomized trial of 80% vs 30% inspired supplemental oxygen in the operative and perioperative period, we found that 80% supplemental oxygen reduced the risk of SSI by 39%. When controlling for multiple contributing factors, the reduction in SSI risk associated with 80% FIO_2 was nearly 54%. Patients with infections had significantly longer hospital stays and delays to ambulation. This observed risk reduction was similar to the 2-fold reduction reported by Greif et al[6] in 500 patients and also consistent with the study by Hopf et al,[5] showing that infection risk is inversely related to tissue oxygenation. In contrast, a recent study by Pryor et al[7] with only 160 patients reported that supplemental oxygen increases the risk of infection. It is thus worth considering why the results of Pryor et al differ so markedly from other available data.

Pryor et al[7] did not specify the baseline infection rate they used, making it impossible to confirm their estimate that

Table 1. Patient Characteristics in the Study Analysis* (cont)

	30% FIO_2 (n = 143)	80% FIO_2 (n = 148)
Preoperative values		
Risk scores (% patients)#		
SENIC		
1	22 (15.4)	29 (19.4)
2	106 (74.1)	95 (64.2)
3	15 (10.5)	24 (16.2)
NNISS		
0	18 (12.6)	25 (16.9)
1	98 (68.5)	86 (58.1)
2	27 (18.9)	37 (25.0)
Clinical data, mean (SD)		
Systolic BP, mm Hg	133 (18)	134 (20)
Diastolic BP, mm Hg	77 (11)	75 (11)
Heart rate, beats/min	75 (12)	75 (11)
Respiratory rate, breaths/min	14.7 (2.7)	14.7 (2.4)
Core temperature, °C	36.5 (0.4)	36.5 (0.3)
PaO_2, mm Hg		
1-h postinduction	117.5 (40.6)	285.9 (96.6)†
2-h postinduction	125.4 (49.0)	233.7 (89.7)†
Laboratory values, mean (SD)		
Hemoglobin, g/L	131 (19)	129 (19)
White blood cell count, /μL	7158 (1971)	7621 (2393)
Lymphocytes, /μL	1935 (747)	1918 (759)
Glucose, mg/dL	101 (19)	101 (23)
Blood urea nitrogen, mg/dL	34 (14)	36 (12)
Creatinine, mg/dL	1.03 (0.78)	0.97 (0.33)
Bilirubin, mg/dL	0.68 (0.45)	0.68 (0.61)
Proteins, g/L	68 (7)	68 (8)
Albumin, g/L	39 (5)	39 (5)
aPTT, s	12.6 (1.4)	12.7 (3.2)
Fibrinogen, μg/L	12.2 (4.2)	11.4 (4.1)
Platelets, $\times 10^3$/μL	265 (87)	277 (97)
Postoperative values		
Patients receiving transfusions	19 (16)	23 (13)
Units per patient, mean (SD)	2.0 (1.1)	3.1 (2.0)
Blood loss, mean (SD), mL	141 (254)	144 (311)
Hemoglobin, mean (SD), g/L	11.5 (2.5)	11.0 (1.2)†
Glucose, mean (SD), mg/dL**	110.2 (20.9)	113.2 (24.5)

Abbreviations: aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; FIO_2, fraction of inspired oxygen; NNISS, National Nosocomial Infections Surveillance System; PaO_2, partial pressure of oxygen; SENIC, Study on the Efficacy of Nosocomial Infection Control.

SI conversions: To convert bilirubin to μmol/L, multiply by 17.1; creatinine to μmol/L, multiply by 88.4; and glucose to mmol/L, multiply by 0.0555.

*Data are presented as No. (%) unless otherwise specified.

†P<.05.

‡Includes volvulus syndrome, diverticulitis, polyposis, and bridles.

§ASA I indicates a healthy patient; ASA II, a patient with mild systemic disease; and ASA III, a patient with severe systemic disease.

‖History of ear, nose, and throat; eye; and psychiatric problems.

¶Includes laparotomy, colostomy, reconstruction of Hartmans operation, segmentary resections, and combined procedures.

#With the SENIC scoring system, 1 point each is assigned for the presence of 3 or more diagnoses, surgery lasting 2 hours or more, surgery at an abdominal site, and the presence of a contaminated or infected wound. The NNISS scoring system, a risk index score ranging from 0 to 3, is the number of risk factors present among the following: a patient with an ASA preoperative assessment score of 3, 4, or 5; an operation classified as contaminated or dirty-infected; and an operation lasting over T hours, where T depends on the operative procedure being performed.

**Postoperative glucose concentrations are the means of measurements taken on postoperative days 1, 4, 7, 10, and 14.

300 patients would be required to detect a 40% reduction in the infection rate. But to have an 80% power to detect the 40% risk reduction that they specified from 25% (our baseline) or from 11% (baseline by Greif et al[6]) would require 540 or 651 patients, respectively; and to detect a 40% increase would require 698 or 930 patients, respectively. The study thus appears to have been underpowered and then stopped after only 160 patients were randomized. The authors specify that 160 patients was an a priori stopping point, although 53.3% of the anticipated sample size is a curious a priori stopping point.

A second limitation is that the treatment groups in the study by Pryor et al[7] were not homogeneous. For example, in their study, patients assigned to 80% oxygen weighed more and were more than twice as likely to have a body mass index (calculated as weight in kilograms divided by the square of height in meters) exceeding 30. Patients assigned to 80% oxygen also had longer operations, lost significantly more blood, and required significantly more fluid replacement. Furthermore, Pryor et al[7] failed to control many variables believed to influence infection risk, including anesthetic, fluid, antibiotic, and pain treatment. In contrast, characteristics of the patients we randomized to each treatment group were comparable, aside from minor differences in height and sex, neither of which is known to influence infection risk.

A third limitation of the study by Pryor et al[7] is that wound infections were determined by retrospective chart review; a review that was apparently conducted by unblinded investigators. This insensitive method contrasts markedly with the daily blinded wound evaluations used in our study and in the study by Greif et al.[6] It is possible that these method problems contributed to a result that is inconsistent with considerable in vitro, in vivo, and clinical data.

All surgical wounds become contaminated to some degree. The primary determinant of whether contamination is established as a clinical infection is host defense. Host defense is most critical during a decisive period lasting a few hours after contamination. For example, antibiotics ameliorate infections and hypoperfusion aggravates infections only during the first few hours after contamination.[15] The decisive period for oxygen remains unknown but may be far longer than for antibiotics. Our patients were maintained at the designated oxygen concentration during surgery and for 6 postoperative hours. In contrast, Greif et al[6] provided supplemental oxygen for only 2 postoperative hours. The results, however, were nearly identical, which suggests that 2 hours may be sufficient. Only a direct comparison within a single study will identify the optimal postoperative duration of supplemental oxygen therapy. As an exploratory analysis, we considered the relationship of tobacco smoking and SSI. Tis-

Table 2. Comparative Outcomes Between High and Low F_{IO_2} Groups

	30% F_{IO_2} (n = 143)	80% F_{IO_2} (n = 148)	*P* Value*
No. of patients (%)			
Surgical site infection	35 (24.4)	22 (14.9)	.04
Daily ASEPSIS score ≥20 at any time	37 (25.9)	25 (16.9)	.06
ICU admission	5 (3.5)	4 (2.7)	.74
Time after surgery, mean (SE), d			
Bowel function	3.1 (1.7)	3.0 (1.5)	.54
First solid food intake	4.4 (2.0)	4.2 (2.2)	.57
Walking	4.2 (2.6)	3.9 (2.2)	.28
Staples removed	10.3 (3.0)	10.5 (3.6)	.71
Hospitalization after surgery	10.5 (4.4)	11.7 (7.0)	.09

Abbreviations: ASEPSIS, scoring system (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, and duration of inpatient Stay); F_{IO_2}, fraction of inspired oxygen; ICU, intensive care unit.
*Wound infections and ICU admission were compared with Mann-Whitney *U* tests; other data were compared with unpaired *t* tests.

Table 3. Factors Associated With Surgical Site Infection (Adjusted and Unadjusted Analysis)*

	RR (95% CI)	
	Unadjusted Univariate Analysis	Adjusted Multivariate Analysis†
80% F_{IO_2}	0.61 (0.38-0.98)	0.46 (0.22-0.95)
Male sex	1.95 (1.06-3.61)	2.04 (0.87-4.79)
Weight per kg	1.01 (0.99-1.04)	1.01 (0.98-1.04)
Age per y	1.01 (0.99-1.04)	1.02 (0.98-1.05)
Respiratory disease	2.15 (1.03-4.48)	3.23 (1.18-8.86)
Allergy	0.38 (0.08-1.69)	0.41 (0.10-1.72)
Preoperative hemoglobin per g/L	1.15 (0.99-1.35)	1.07 (0.88-1.31)
Preoperative glucose per mg/dL	1.01 (0.99-1.02)	1.01 (0.99-1.02)
SENIC score‡		
1	1.00	1.00
2	1.13 (0.59-2.17)	1.02 (0.36-2.91)
3	1.16 (0.49-2.74)	2.02 (0.45-9.13)
Smoking status		
Nonsmoker	1.00	1.00
<20 cigarettes/d	1.44 (0.62-3.32)	1.68 (0.60-4.72)
≥20 cigarettes/d	1.34 (0.45-3.99)	0.79 (0.20-3.06)

Abbreviations: CI, confidence interval; F_{IO_2}, fraction of inspired oxygen; RR, relative risk; SENIC, Study on the Efficacy of Nosocomial Infection Control.
SI conversions: To convert glucose to mmol/L, multiply by 0.0555.
*Categorical variables include F_{IO_2}, male sex, respiratory disease, allergy, SENIC score, and tobacco smoking. Continuous variables include weight, age, preoperative hemoglobin, and preoperative glucose concentration.
†See "Methods" for list of all variables included in the multivariate analysis.
‡With the SENIC scoring system, 1 point each is assigned for the presence of 3 or more diagnoses, surgery lasting 2 hours or more, surgery at an abdominal site, and the presence of a contaminated or infected wound.

sue oxygenation decreases significantly for 1 hour after cigarette smoking[16] and it has been suggested that smokers have a higher infection risk.[2,17,18] Consistent with recent studies,[6,19] however, we found no significant increase in the risk of infection among smokers. One explanation for this finding is that the effect of smoking on tissue oxygenation is time-limited. Because patients are no longer allowed to smoke in the hospital, sustained smoking-related reductions in tissue oxygenation may be occurring less frequently.

There are several limitations to our study. The baseline infection rate in our patients was roughly twice that in the study of Greif et al.[6] However, infections are multifactorial and depend on numerous factors, including the type of procedure,[8] duration of anesthetic,[3] control of anesthetic factors, and body temperature.[2] The baseline rate identified in our study was well within values reported in recent series[20,21] and the groups were homogeneous and treated comparably except for the randomized inspired oxygen concentration. Furthermore, the diagnostic method used to describe infection may have affected our results. In the study by Greif et al,[6] infection was considered only when cultures of the wound were positive. However, according to Centers for Disease Control and Prevention criteria, infection can be present without laboratory confirmation and, in our study, the blinded wound evaluator considered any of the following as confirmation of infection: purulent drainage, with or without laboratory confirmation; organisms isolated from an aseptically obtained culture of fluid or tissue; at least 1 of the following signs or symptoms of infection (pain or tenderness, localized swelling, redness, or heat, and the incision was deliberately opened by surgeon, unless incision was culture-negative); or independent diagnosis of incisional SSI by the surgeon or attending physician. Another potential limitation is that we only considered infections that occurred in the first 15 days after operation and may have missed subsequent infectious events. Previous studies[2,5,6] indicate that wound infections are usually detected within this time frame; however, 70% of the wound infections in the study by Grief et al[6] were detected in the first 10 days after surgery.[22]

In conclusion, supplemental 80% FIO_2 during and for 6 hours after major colorectal surgery reduced postoperative wound infection risk by roughly a factor of 2. This result is consistent with most available in vitro data and 1 other appropriately designed RCT.[6] Supplemental oxygen appears to confer few risks to the patient, has little associated cost, and should be considered part of ongoing quality improvement activities related to surgical care.

Author Contributions: Dr Belda had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Belda, Garcia de la Asuncion, Sessler.
Acquisition of data: Belda, Aguilera, Garcia de la Asuncion, Alberti, Vicente, Ferrandiz, Rodriguez, Company, Aguilar, Botello, Orti.
Analysis and interpretation of data: Belda, Aguilera, Vicente, Rodriguez, Company, Sessler, Orti.
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Critical revision of the manuscript for important intellectual content: Belda, Alberti, Sessler.
Statistical analysis: Belda, Alberti, Vicente, Company, Sessler, Orti.
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There are many ways of educating our feelings, but I recommend reading as that which is most ready to hand.
—Robertson Davies (1913-1995)

acteristics such as size, mobility, extent, and location, the subject remains incompletely understood. The effect of vegetation size on the risk of embolization was addressed in a meta-analysis of 10 studies involving 738 patients.[3] In this meta-analysis, the risk of embolization in patients with vegetations more than 1cm in size was almost 3 times higher than in those patients with nondetectable or small vegetations (odds ratio, 2.90; 95% confidence interval, 1.95-4.02). Sanfilipo et al[4] evaluated 219 patients with vegetations and found that prolapsing vegetations and involvement of extravalvular structures increased the risk of stroke. The location of valvular involvement may also have prognostic significance, with mitral valve associated with higher rates of stroke than aortic valve, and anterior leaflet associated with higher rates than posterior leaflet.[5] In addition to collecting the clinical data on our patients, ICE-PCS maintains a core laboratory in which echocardiograms from enrolled patients are stored. We will be able to address the issue of echocardiographic predictors as well as interobserver variation in interpretation, a potentially important confounder in these investigations.[6]

Dr Lorber inquired about the low reported rates of dental procedures antedating episodes of viridans group streptococcal IE in our study. The data compiled within the ICE-PCS do indeed suggest that a significant proportion of the viridans streptococcal IE cases from this multinational cohort occurred in the absence of recent dental work. This finding is consistent with prior reports demonstrating that only 4% to 19% of cases of endocarditis are attributable to dental and other health care procedures.[7-9] We are conducting analyses to evaluate the role of these procedures on the development of endocarditis in the ICE-PCS cohort.

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CORRECTIONS

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Incorrect Data in Table: In the Editorial entitled "The IDEAL Cholesterol: Lower Is Better" published in the November 16, 2005, issue of *JAMA* (2005;294:2492-2494), 2 incorrect percentages were given in the Table. The risk reduction for the end point of coronary heart disease death or myocardial infarction in the Treating to New Targets (TNT) study was 22%, not 21%. Also, the risk reduction for this same end point in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study was 12%, not 11%.